Understanding mania in bipolar disorder: perspectives on causation and pathogenesis

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Abbreviations

AC	Anticonvulsant
AD	Antidepressant
ADAS-Cog	Alzheimer's Disease Assessment Scale-cognitive subscale
ADHD	Attention Deficit Hyperactivity Disorder
AED	Antiepileptic Drug
AMIPB	Adult Memory and Information Processing Battery
AMPA	α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid
ANX	Anxiety
AP	Antipsychotic
ASD	Autism Spectrum Disorder
BD	Bipolar Disorder
BD-I	Bipolar Disorder Type I
BD-II	Bipolar Disorder Type II
BVRT	Benton Visual Retention Test
BZD	Benzodiazepine
CAM	Complementary and Alternative Medicine
CANTAB	Cambridge Neuropsychological Test Automated Battery
CAVLT	California Verbal Learning Task
CBZ	Carbmazepine
CPT	Continuous Performance Test

CPT	Carnitine palmitoyltransferase I (CPT I) deficiency
CVLT	California Verbal Learning Test
DCS-R	Diagnosticum für Cerebralschädigung-II
DEP	Depression
EEG	Electroencephalogram
FS	Focal Seizures
fMRI	Functional Magnetic Resonance Imaging
GABA	gamma-Aminobutyric acid
HAM-D	Hamilton Depression Rating Scale
HC	Healthy Controls
HM	Herbal Medicine
ILAE	International League Against Epilepsy
IQ	Intelligence Quotient
KD	Ketogenic Diet
KYNA	Kynurenic acid
LCAD	Long-chain acyl dehydrogenase deficiency
LFS	Focal Seizures Left Sided Foci
Li	Lithium
LTG	Lamotrigine
LTL	Left Temporal Lobe
Mono	Monotherapy
MCAD	Medium-chain acyl dehydrogenase deficiency
MCT	Medium Chain Triglyceride

MRI	Magnetic Resonance Imaging
MS	Mood Stabilizer
NAART	North American Adult Reading Test
NREM	Non-Rapid Eye Movement
PERT	Penn Emotion Recognition Test
PET	Positron Emission Tomography
Poly	Polytherapy
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PS	Partial Seizures
OCD	Obsessive Compulsive Disorder
RAVLT	Rey Auditory Verbal Learning Test
REM	Rapid Eye Movement
RFS	Focal Seizures Right Sided Foci
RTL	Right Temporal Lobe
SCAD	Short-chain acyl dehydrogenase deficiency
SPD	Sprague-Dawley
SZ	Schizophrenia
TMT	Trail Making Test
RAVLT	Rey Auditory Verbal Learning Task
ROCFT	Rey Complex Figure Test
UPSIT	University of Pennsylvania Smell Identification Test
UTAS	University of Tasmania
VLMT	Verbaler Lern- und Merkfähigkeitstest

VPA	Valproate
WAIS	Wechsler Adult Intelligence Scale
WTAR	Wechsler Test of Adult Reading
WCST	Wisconsin Card Sorting Task
WMS	Wechsler Memory Scale
WRAT	Wide Range Achievement Test
YMRS	Young Mania Rating Scale

Abstract

The cardinal feature of bipolar disorder type I (BDI) is mania. Episodes of mania may lead to marked impairments in social and occupational functioning and impose a significant financial burden on both patient and health-care system. In order to alleviate this burden a more detailed understanding of the aetiology and pathogenesis of mania is important to direct development of improved treatments.

Chapter 1 is an introduction to the psychopathology, course, antecedents, precipitants, treatment response and pathogenesis of mania in bipolar disorder type I. Understanding of the underlying pathophysiology of mania is limited. The thesis identifies a series of studies based on review methodologies that bring together four perspectives on the causes and processes involved in episodes of mania. These perspectives comprise:

Comparison of mania with a reference condition, namely partial seizures arising from the temporal lobe (PS) as a strategy for identifying localising pathways in the brain based on precipitating factors in common between the two conditions;

Comparison of cognitive deficits between illness episodes in BD and temporal lobe epilepsy (TLE), to cast light on the underlying neuropsychological substrates that may indicate vulnerability and brain pathology;

Treatment response of mental disorders to an evidence-based therapy used in epilepsy, the ketogenic diet; and

Examination of a subset of substance-induced mania, that was reported in association with the use of herbal medicines.

The second part of chapter 1 is an introduction to temporal lobe epilepsy (note: the nomenclature temporal lobe epilepsy (TLE) is synonymous with partial seizures (PS) or focal seizures (FS) arising from the temporal lobe, the term used in this thesis depends on the most common usage in the literature being reviewed). The third part introduces the studies, presented as four papers published in refereed journals, which follow in chapters 2 to 5.

Chapter 2 presents a published paper that considers precipitating factors of recurrent episodes of mania. It identifies common precipitating factors for mania and partial seizures in TLE (PS) as stress, sleep deprivation, antidepressant medication and, tentatively, emotion; for mania alone, goal-attainment events, spring and summer season, postpartum, and drugs including steroids and stimulants; for PS alone, winter season, menstruation and specific

triggers in complex reflex epilepsies. The overlap of precipitating factors in mania and PS implies that common brain processes may contribute to both, consistent with findings from neuroscience research regarding mechanisms, which are discussed in detail.

Chapter 3 presents a published paper comprising a systematic review and comparison of cognitive function in euthymic BD-I and pre-surgical TLE. It is important to consider inter-episode BD in order to better understand the neurobiological substrates involved in the propensity to mania. This review concludes that both disorders exhibit deficits in executive function and verbal memory suggestive of both frontal and temporal lobe involvement.

Chapter 4 presents a published paper regarding the status of the ketogenic diet as a treatment in mental disorders. There is a well-established overlap in medications for BD and epilepsy, particularly with mood stabilizers such as sodium valproate. An evidence-based treatment for epilepsy, the ketogenic diet (KD) has received limited attention in mental disorders. In BD, the mechanism by which KD may be effective is based on the hypothesis that acidosis achieved through ketosis reduces intra-cellular sodium, calcium, both of which are elevated in the disorder. Mood stabilizers reduce intra-cellular sodium in an activity-dependant manner within the context of KD, through acidification of the blood. The literature regarding KD in mental disorders was reviewed and included studies on anxiety, depression, bipolar disorder, schizophrenia, autism spectrum disorder and attention deficit hyperactivity disorder. This identified the need for carefully controlled research to resolve whether KD has therapeutic potential in mental disorders and the potential utility of direct ketone supplementation (as opposed to a restrictive diet inducing ketosis) as a treatment modality.

Chapter 5 presents a published paper examining case reports of substance-induced mania specifically associated with use of herbal medicines (HM). All case reports (n=35) were associated with use rather than withdrawal of HM. Causal attributions are problematic given the paucity of reports, antidepressant co-prescribing in 12 cases, inclusion of 7 cases with a past diagnosis of mania, insufficient data regarding pattern and type of HM use, and lack of a reference frequency of spontaneous mania. Putative pathophysiological mechanisms for each reported HM inducing mania are discussed. These centre on HPA-axis activation and increased monoamine activity.

Chapter 6 Discusses the findings of chapters 2 to 5, concluding that the use of multiple perspectives and the reference condition of TLE identifies leads that may enhance understanding of basic mechanisms involved in episodes of mania. Directions for future research arising from the results are outlined.

Chapter 1

Introduction and Thesis Overview

This introductory chapter provides an overview of mania in bipolar disorder (BD) with respect to classification, rating scales, management, aetiological factors, pathways, brain activation and neural substrates. The aim of this thesis is to study the aetiology and pathogenesis of mania in BD which is important to direct developments for improved treatments in individuals with BD. Aetiology may be defined as "the cause, set of causes, or manner of causation of a disease or condition (Oxford Dictionaries 2019)". Aetiology is synonymous with causation and in this thesis the terms are used interchangeably. Pathogenesis may be defined as "the manner of development of a disease (Oxford Dictionaries 2019)". It is noted that aetiology may represent the composite effects of many risk factors and precipitants with complex interactions, potentially feeding into final common pathways. Furthermore, there are many nuances and uncertainties in the diagnostic process. This introductory chapter indicates the main aetiological factors that are currently recognised.

Following this, a novel approach to investigating aetiology is proposed, namely the comparison of mania and temporal lobe epilepsy (TLE). TLE has a localizing pathology and is introduced as a potentially informative reference condition for comparison with mania. An overview of TLE covers the temporal lobes, comparison of mania to TLE as a reference condition, psychiatric comorbidities in epilepsy, BD and epilepsy similarities, treatment overlaps and prevalence of BD in epilepsy. The third part of this chapter provides an introduction to the published papers which address precipitating factors, neurocognition, the ketogenic diet and herbal medicine associated manias.

1.1.1 An overview of mania

BD and mania have been recorded throughout history. Soranus of Ephesus (98-177AD) made the distinction between mania and melancholia and accorded them separate aetiologies in humoral theory (Marneros and Goodwin 2005). Falret, a French psychiatrist, categorized what we now know as BD as "folie circulaire" which included manic and melancholic episodes

punctuated by symptom-free intervals (Falret 1854). Baillarger used the term “folie à double forme” to describe manic-melancholic episodes (Baillarger 1880). Kraepelin (1921) differentiated schizophrenia and manic-depressive psychosis (MDP) on the basis of course of illness with MDP being characterized as episodic with interepisode recovery compared to a chronic deteriorating course in schizophrenia. The “circular” nature of the illness formed the prototype of a larger group of periodic psychoses encompassing periodic mania, melancholia and cyclic disorders (Angst and Sellaro 2000). Hence the concept of BD has exhibited both commonalities and differing points of emphasis over time. With the advent of syndromal diagnosis in the official nomenclature of DSM-III, the conceptualization of BD has become reified as a matter of convention based on a mathematical model of weights and value judgements as to essential criteria. This does not do justice to concerns as to what represent the core features of the illness, for example whether mood or vegetative symptoms are the more essential features with respect to the biological underpinnings of the illness. This is further emphasised by the inter-rater reliability coefficients for diagnosis of the presence of BD. Field trials of the iterations of DSM over the past three decades typically quote Kappa coefficients for inter-rater agreement of 0.56 (de Dios 2014).

The occurrence of at least one episode of mania is required for a diagnosis of BD. Commonly reported signs and symptoms of mania include mood elevation or dysphoria, irritability, grandiosity, motor activation, accelerated thought processes, pressured speech, decreased need for sleep, irritability, distractibility and mood lability (Cassidy, Forest et al. 1998). In the acute manic phase, poor insight is a defining characteristic (Ghaemi, Stoll et al. 1995). The diagnostic classification of BD includes: bipolar disorder type I (BDI), which requires at least one episode of mania; bipolar disorder type II (BDII), which requires at least one episode each of hypomania and depression; substance/medication-induced bipolar and related disorder; and secondary mania caused by drugs, infection, neoplasm, epilepsy, and

metabolic disturbances. Krauthammer and Klerman view mania as a syndrome with multiple causes, and that the notion of secondary mania casts doubt on any unitary or single-agent hypothesis of the aetiology of mania supporting the concept of a continuum of psychopathologic syndromes (Krauthammer and Klerman 1978). Whether primary or secondary in origin, episodes of mania may lead to impairments in social and occupational functioning and impose a significant financial burden.

1.1.2 Diagnosis of mania and bipolar disorder

The development and categorization of diagnostic criteria allow clinicians to delineate healthy and pathological mental processes and behaviours (Kaltenboeck, Winkler et al. 2016). Diagnoses may be classified using the Diagnostic and Statistical Manual of Mental Disorders 5th Edition (DSM-5) or the International Classification of Diseases (ICD-10).

DSM-5 diagnostic criteria for a manic episode

To obtain a diagnosis of BD there must have been one or more episodes of mania with or without depression at another point in time. According to the DSM-5, episodes of mania consist of several specifiers including the following criteria:

A: A distinct period of abnormally and persistently elevated, expansive, or irritable mood and abnormally and persistently increased activity or energy, lasting at least one week and present most of the day, nearly every day (or any duration if hospitalization is necessary).

B: During the period of mood disturbance and increased energy or activity, three (or more) of the following symptoms (four if the mood is only irritable) are present to a significant degree and represent a noticeable change from usual behaviour:

1. Inflated self-esteem or grandiosity
2. Decreased need for sleep (e.g., feels rested after only three hours of sleep)
3. More talkative than usual or pressure to keep talking
4. Flight of ideas or subjective experience that thoughts are racing

5. Distractibility (i.e., attention too easily drawn to unimportant or irrelevant external stimuli), as reported or observed

6. Increase in goal-directed activity (either socially, at work or school, or sexually) or psychomotor agitation (i.e., purposeless non-goal-directed activity)

7. Excessive involvement in activities that have a high potential for painful consequences (e.g., engaging in unrestrained buying sprees, sexual indiscretions, or foolish business investments)

C: The mood disturbance is sufficiently severe to cause marked impairment in social or occupational functioning or to necessitate hospitalization to prevent harm to self or others, or there are psychotic features.

D: The episode is not attributable to the physiological effects of a substance (e.g., a drug of abuse, a medication, other treatment) or to another medical condition (American Psychiatric Association 2013).

DSM-5 diagnostic criteria for a hypomanic episode

Criteria A through F constitute a hypomanic episode. Hypomanic episodes are common in bipolar I disorder but are not required for the diagnosis of bipolar I disorder.

A. A distinct period of abnormally and persistently elevated, expansive, or irritable mood and abnormally and persistently increased activity or energy, lasting at least four consecutive days and present most of the day, nearly every day.

B. During the period of mood disturbance and increased energy and activity, three (or more) of the following symptoms (four if the mood is only irritable) have persisted, represent a noticeable change from usual behaviour, and have been present to a significant degree:

1) Inflated self-esteem or grandiosity.

2) Decreased need for sleep (e.g., feels rested after only three hours of sleep).

3) More talkative than usual or pressure to keep talking.

4) Flight of ideas or subjective experience that thoughts are racing.

5) Distractibility (i.e., attention too easily drawn to unimportant or irrelevant external stimuli), as reported or observed.

6) Increase in goal-directed activity (either socially, at work or school, or sexually) or psychomotor agitation.

7) Excessive involvement in activities that have a high potential for painful consequences (e.g., engaging in unrestrained buying sprees, sexual indiscretions, or foolish business investments).

C. The episode is associated with an unequivocal change in functioning that is uncharacteristic of the individual when not symptomatic.

D. The disturbance in mood and the change in functioning are observable by others.

E. The episode is not severe enough to cause marked impairment in social or occupational functioning or to necessitate hospitalization. If there are psychotic features, the episode is, by definition, manic.

F. The episode is not attributable to the physiological effects of a substance (e.g., a drug of abuse, a medication, or other treatment).

NOTE: A full hypomanic episode that emerges during antidepressant treatment (e.g., medication, electroconvulsive therapy) but persists at a fully syndromal level beyond the physiological effect of that treatment is sufficient evidence for a hypomanic episode diagnosis. However, caution is indicated so that one or two symptoms (particularly increased irritability, edginess, or agitation following antidepressant use) are not taken as sufficient for a diagnosis of a hypomanic episode, nor necessarily indicative of a bipolar diathesis.

DSM-5 diagnostic criteria for substance/medication-induced bipolar and related disorder

A. A prominent and persistent disturbance in mood that predominates in the clinical picture and is characterized by elevated, expansive, or irritable mood, with or without depressed mood, or markedly diminished interest or pleasure in all, or almost all, activities.

B. There is evidence from the history, physical examination, or laboratory findings of both (1) and (2):

1. The symptoms in Criterion A developed during or soon after substance intoxication or withdrawal or after exposure to a medication.
2. The involved substance/medication is capable of producing the symptoms in Criterion A.

C. The disturbance is not better explained by a bipolar or related disorder that is not substance/medication-induced. Such evidence of an independent bipolar or related disorder could include the following:

The symptoms precede the onset of the substance/medication use; the symptoms persist for a substantial period of time (e.g., about 1 month) after the cessation of acute withdrawal or severe intoxication; or there is other evidence suggesting the existence of an independent non-substance/medication-induced bipolar and related disorder (e.g., a history of recurrent non-substance/medication-related episodes).

D. The disturbance does not occur exclusively during the course of a delirium.

E. The disturbance causes clinically significant distress or impairment in social, occupational, or other important areas of functioning.

The World Health Organization's International Classification of Diseases (ICD-10) provides the following descriptions and definitions:

The ICD-10 Mood [affective] disorders

The category of mood [affective] disorders appears in sections F30-F39 and "contains disorders in which the fundamental disturbance is a change in affect or mood to depression (with or without associated anxiety) or to elation. The mood change is usually accompanied by a change in the overall level of activity; most of the other symptoms are either secondary to, or easily understood in the context of, the change in mood and activity. Most of these disorders tend to be recurrent and the onset of individual episodes can often be related to stressful events or situations." In addition hypomanic or manic episodes in individuals who have had one or more previous affective episodes (depressive, hypomanic, manic, or mixed) should be coded as bipolar affective disorder (World Health Organization 1992).

ICD-10 criteria for a manic episode

All the subdivisions of this category should be used only for a single episode. Hypomanic or manic episodes in individuals who have had one or more previous affective episodes (depressive, hypomanic, manic, or mixed) should be coded as bipolar affective disorder. A manic episode is characterized by a persistent elevation of mood, increased energy and activity, and usually marked feelings of well-being and both physical and mental efficiency. Increased sociability, talkativeness, over-familiarity, increased sexual energy, and a decreased need for sleep are often present but not to the extent that they lead to severe disruption of work or result in social rejection. Irritability, conceit, and boorish behaviour may take the place of the more usual euphoric sociability. The disturbances of mood and behaviour are not accompanied by hallucinations or delusions.

1.1.3 Prevalence, incidence and course of bipolar disorder

Reported prevalence estimates from the 2007 United States National Comorbidity Survey Replication study (n = 9,282) were lifetime (and 12-month shown in parentheses) prevalence 1.0% (0.6%) for bipolar type I disorder (BDI), 1.1% (0.8%) for bipolar type II disorder (BDII) and 2.4% (1.4%) for subthreshold BD (which refers to recurrent hypomania without a major

depressive episode or with fewer symptoms than required for threshold hypomania) (Merikangas, Akiskal et al. 2007). In a population-based cohort study (n= 800,000), it was found that the overall incidence rates (IR) of BD was 0.70/10,000 person-years (95% CI 0.57-0.83) the IR rate of BDI was 0.43/10,000 person-years (95% CI 0.34-0.55) and the IR of BDII was 0.19/10,000 (95% CI 0.13-0.55) (Kroon, Wohlfarth et al. 2013).

BD is a chronic disorder with episodic manifestations of mania and depression. The frequency of episodes varies widely between cases with inter-episode euthymia or normal mood. The time points that have been used to determine age of onset include the following: age at first treatment, age of first hospitalization, or the first time that the diagnostic criteria are met (Saunders and Goodwin 2010). Childhood onset is recognized but is controversial. The peak onset of BDI is distributed across three age brackets including 17.4 years (*SD* = 2.3), 25.1 years (*SD* = 6.2), and 40.4 years (*SD* = 11.3) (Bellivier 2003). A significant proportion of patients with BDI do not receive treatment for their first episode of either major depression, mania or a mixed state (Chengappa, Kupfer et al. 2003). The polarity at onset of first episode has been examined and depressive episodes were the most common followed by mixed or manic episodes (Perugi, Micheli et al. 2000).

The longitudinal weekly symptomatic course of patients with BDI (n=146) was examined by Judd et al. (2002). According to self-report results participants were symptomatic 47.3% of weeks throughout a mean of 12.8 years of follow-up. Depressive symptoms (31.9% of total follow-up weeks) predominated over manic/ hypomanic symptoms (8.9%) or cycling/mixed symptoms (5.9%)(Judd 2002). Mania is typically of abrupt onset and the mean duration is 13 weeks though this may vary widely (Solomon, Leon et al. 2010). In a small percentage of patients, illness may be confined to one episode of mania in a lifetime or be continuous over years. Frank et al. (1991) illustrated the course of BD in two figures including

remission, recovery, relapse, switch and recurrence in mania (Figure 1) and depression (Figure 2).

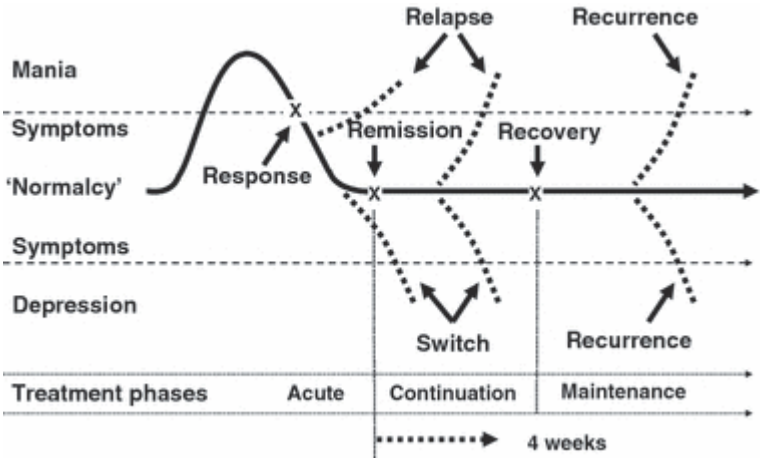

Figure 1. Diagram showing manic symptoms, remission and recovery (Frank 1991)

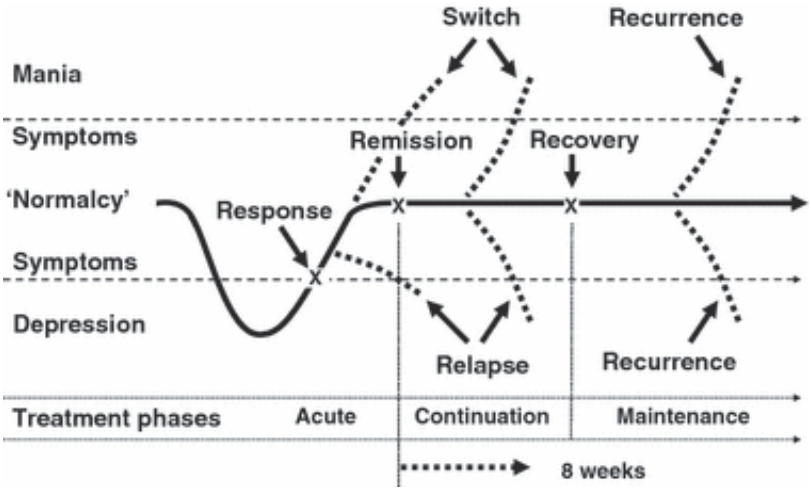

Figure 2: Remission, recovery, relapse, switch, and recurrence in depressive episodes (Frank 1991)

The ability to chart fluctuations in the course of BD is reliant on the valid and accurate measurement of signs and symptoms of the presenting illness. The severity of a manic episode

may be quantified by using the Young Mania Rating Scale (YMRS) which is the most frequently used rating scale to assess manic symptoms. It is an 11-item clinician-administered rating scale with high validity (Young, Biggs et al. 1978). This measure considers various aspects of the presentation of mania such as elevated mood, increased motor activity/ energy, sexual interest, sleep, irritability, speech (rate and amount), language/thought disorder, content, disruptive/aggressive behaviour, appearance and insight, which together provide a clinically relevant picture of mania (YMRS=12).

The Altman Self-Rating Mania Scale (ASRM) is a self-reported diagnostic scale which consists of 5 items to assess the presence and severity of hypomanic or manic symptoms. The five areas assessed include: positive mood, self-confidence, sleep patterns, speech patterns and amount of motor activity. Each item is assessed on a 4-point Likert scale whereby 0 is normal and 4 is overtly manic. The measure has been shown to be valid and reliable, to have good test-retest reliability in patients with mania or depression and is sensitive to change after treatment (Altman, Hedeker et al. 1997). It may be useful in wide scale studies. It is noted that self-report scales may be subject to the over-reporting or under-reporting of symptoms by patients or participants. According to Cassidy, the YMRS and the ASRM provide variable coverage of classic mania symptoms including sleep, psychosis and sexuality and poor coverage of dysphoric features. No standardized rating scale to measure the manic state has emerged by consensus in the field (Cassidy et al. 1998).

A further aspect of the course of the illness is response to treatment which may involve the same pathways as are triggered in the aetiology of the illness. According to the Canadian Network for Mood and Anxiety Treatments (CANMAT) and the International Society for Bipolar Disorders (ISBD) guidelines for the management of patients with BD, treatments for manic and depressive phases differ. For acute mania, lithium, valproate, and several atypical antipsychotics continue to be first-line treatments. For the management of bipolar depression,

lithium, lamotrigine, and quetiapine monotherapy, olanzapine plus selective serotonin reuptake inhibitor (SSRI), and lithium or divalproex plus SSRI/bupropion remain first-line options (Yatham, Kennedy et al. 2009). Lithium, lamotrigine, valproate, and olanzapine continue to be first-line options for maintenance treatment of BD. However, treatments have side effects and are not effective in all patients indicating heterogeneity of the condition.

1.1.4 Aetiological factors in bipolar disorder

Aetiology is commonly classified in terms of predisposing, precipitating and perpetuating factors, all of which are highly relevant to understanding the onset and course of a disorder. The precise pathogenesis of BD is unknown, though it is generally agreed that its development is influenced by genetic and environmental factors (Craddock and Jones 1999) and diagnosis is based on signs and symptoms as noted above in section 1.1.2. The variance in BD attributed to heritability is reported to be between 60-93%, more recent analyses tending to be at the higher range (Barnett and Smoller 2009). In addition, a range of other reported risk factors include inflammation and maternal or fetal infections (Avramopoulos 2015), cannabis use (Lagerberg, Sundet et al. 2011), obstetric complications (Kinney, Yurgelun-Todd et al. 1993), season of birth (Castrogiovanni, Iapichino et al. 1998) and childhood trauma (Etain, Henry et al. 2008). Together these account for less than 10 % of the variance in occurrence of BD (Marneros 2007).

With respect to genetics, family studies have noted that first-degree relatives of BD patients have an excess risk of the disorder, while twin studies (combined with adoption studies) suggest that genes are largely responsible for this familial aggregation (Smoller 2003). McQueen et al. found genome-wide significant linkage to chromosomes 6q and 8q and suggestive linkage to chromosomes 9p and 20p (McQueen 2005). In a genome-wide association analysis in cases of BD (n=4,387) and controls (n=6,209) a region of strong association was identified in ANK3 (ankyrin G) and CACNA1C (alpha 1C subunit of the L-

type voltage-gated calcium channel) suggesting that ion channelopathies may be involved in the pathogenesis of BD (Ferreira 2008). In a recent study by Charney et al. (2017) of BD patients (n=6447) relative to control participants (n=12639) eight genome-wide significant loci, including a novel locus on chromosome 10 were identified. Two coding genes, adducin 3 (ADD3) and aminopeptidase P (XPNPEP1) and a non-coding RNA also annotated as an antisense ADD3 RNA are contained on the new locus. Evidence for genetic heterogeneity between clinical subtypes of BD that is BDI and BDII was also found.

In linkage studies, Craddock and Jones (1999) identified regions of interest including 4p16, 12q23-q24, 16p13, 21q22 and Xq24-q26. In a meta-analysis of whole-genome linkage scans of BD the strongest evidence of susceptibility loci was on 13q (Badner and Gershon 2002). In a whole-genome linkage analysis in a multi-generational family (n=111) with mood disorder including BD Diniz et al. (2017) found that four regions on chromosomes 2p23.1-p22.3, 3p25.3-p24.1, 11p15.4, and 12q24.22-q24.32 achieved genome-wide significance and four regions on chromosomes 1p22.2-p21.2, 1q21.1-q21.3, 12p13.32, and 22q11.21-q12.1 achieved genome-wide suggestive of linkage.

A meta-analysis of identification of pathways for BD was conducted by Nurnberger et al. (2014) who found that among 966 genes, 226 reached statistical significance among these 9 differed in expression in the dorsolateral prefrontal cortex including CACNA1C, DTNA, FOXP1, GNG2, ITPR2, LSAMP, NPAS3, NCOA2, and NTRK3. It was identified that pathways involved in the genetic predisposition to BD include hormonal regulation, calcium channels, second messenger systems, and glutamate signalling. Gene expression studies also implicate neuronal development pathways (Nurnberger, Koller et al. 2014). Studies of the association of rare syndromes with the occurrence of BD have also been informative. Papolos et al. (1996) found a strong association between velo-cardio-facial syndrome and early-onset BD suggestive of a gene deleted at the 22q11 chromosomal locus may be involved in the

pathogenesis of the disorder. Darier's disease, a rare autosomal genetic skin condition associated with BD has been linked to ATP2A2 mutations (Gordon-Smith et al. 2018). The implications of these genetic studies are not sufficiently advanced to form a rigorous understanding of the genetics of BD. The proposed pathways involved in mania derive from the mechanisms of actions of anti-manic agents and abnormalities seen in patients experiencing mania.

1.1.5 Pathophysiology of mania

A number of biological pathways have been implicated in the pathogenesis of mania and reflect our emerging understanding of the complexities of brain functioning. Current and emerging perspectives include the role of genetic mutations and deletions, the modulating effects of epigenetics on gene expression, the role of the microbiome and the role of neuroinflammation. These are generally hypothesised as underlying basic abnormalities or alterations of biology which may become manifest through their effects on brain systems such as neurotransmitters or brain repair mechanisms.

The gene-environment interaction is involved in the pathogenesis of BD. This process includes interaction between the genome, environmental factors and epigenetic marks (Ludwig and Dwivedi 2016). Epigenetics refers to "modifications of the genome that do not alter DNA sequences and are potentially heritable and reversible thus allowing the single genome to adapt its transcriptional repertoire to changing environmental conditions and/ or to create different cell or tissue types in multicellular organisms" (Alam, Abdolmaleky et al. 2017). Changes in DNA methylation in monozygotic twins discordant for mental disorders is of interest as the twins share an almost identical genome even if their pre and post-natal environments differ (McGowan and Szyf 2010). In discordant identical twins with BD, Kuratomi et al (2007) found decreased methylation status of peptidylprolyl isomerase E-like (PPIEL) in the twin with BD. In addition, in female patients with BD compared with female controls, a region upstream of

the spermin synthase (SMS) gene on the X chromosome was significantly hypermethylated. This may affect the heritability of BD and warrants further examination.

In recent years, several discoveries have increased our understanding of the aetiology and pathogenesis of mental disorders, one such factor being the role of the gut. Within the human gastrointestinal tract, there is a variety of microbes (bacteria, archaea, fungi, microbial eukaryotes and virus/phages), known as the microbiota, which are now thought to play pivotal roles in human health. Their genes and metabolic products are known as the microbiome (Allaband, McDonald et al. 2018). There is considerable interest in the microbiome (Allaband, McDonald et al. 2018), with disruptions in this ecosystem linked to several disorders in humans including, Clostridium difficile infection, inflammatory bowel disease, coeliac disease, obesity, colorectal cancer, autism spectrum disorder (Kho and Lal 2018) and BD (Evans, Bassis et al. 2017). Evans et al. compared the stool microbiota of individuals with BD (n=115) relative to controls (n=64) and examined illness severity in those with the disorder (Evans, Bassis et al. 2017). Levels of Faecalibacterium, a key butyrate-producing genus, were decreased relative to controls. Faecalibacterium concentrations were positively associated with better self-reported health outcomes based on the Short Form Health Survey, the Patient Health Questionnaire, the Pittsburgh Sleep Quality Index, the Generalized Anxiety Disorder scale, and the Altman Mania Rating Scale. This suggests that Faecalibacterium may protect against episodes of BD although the precise mechanism is unknown and replication is needed.

Another factor that has increased our understanding of mental disorders is the role of neuroinflammatory and immunological abnormalities which have been found in patients with psychiatric disorders (Najjar and Pearlman 2015). In a meta-analysis of studies comparing BD (n=761) relative to controls (n=919), BD is accompanied by dysregulation of the immune response system (Munkholm, Braüner et al. 2013). The relationship between BD and immune dysfunction has been attributed to a variety of pathophysiological mechanisms including

cytokine-induced monoamine changes, increased oxidative stress, pathological microglial overactivation and HPA axis overactivation (Rosenblat, Gregory et al. 2018). A recent review examined the effects of anti-inflammatory agents in the treatment of manic, depressive and euthymic phases (Rosenblat, Gregory et al. 2018). Promising results have been found in the treatment of depression in BD for anti-inflammatory agents as shown by moderate effect sizes and good tolerability whilst their effects during manic and euthymic phases remain uncertain (Rosenblat, Gregory et al. 2018).

Dopamine was first reported to be involved in the pathophysiology of mania in the 1970s and changes in dopaminergic neurotransmission have been reported to be consistent with abnormalities in BD (Berk, Dodd et al. 2007). Dopamine has been implicated in the pathophysiology of affective syndromes. The dopamine hypothesis suggests that decreased dopamine neurotransmission is involved in the pathogenesis of depression, while increased dopamine activity contributes to the symptoms of mania (Diehl and Gershon 1992). Abler et al. examined the reward activation system in mania and found evidence for abnormal function of the dopamine system during delivery or exclusion of expected rewards in BD. The authors postulated that these deficits in acute mania may aid in our understanding of symptoms of disinhibition and abnormal goal pursuit regulation (Abler, Greenhouse et al. 2008).

Gould and Manji identify Glycogen Synthase Kinase-3 (GSK-3) as a potential molecular target for lithium (Gould and Manji 2005). Lithium inhibits glycogen synthase kinase 3β (GSK-3β) directly or indirectly via stimulation of the kinase Akt-1 (Prickaerts, Moechars et al. 2006). Evidence suggests that the protein kinase C (PKC) signalling cascade may be a similarity for the actions of anti-manic agents, and that excessive PKC activation can disrupt prefrontal cortical regulation of thought and behaviour(Szabo, Machado-Vieira et al. 2009). In a recent review of the role of PKC, several mechanisms such as apoptotic, neoplastic,

inflammatory, energy homeostasis, synaptic neurotransmission, and oxidative balance were thought to be involved in the pathophysiology of BD (Saxena, Scaini et al. 2017).

Others have hypothesised that BD is related to an imbalance between cholinergic and catecholaminergic neuronal activity, as centrally active cholinergic agonists had anti-manic properties (Müller-Oerlinghausen, Berghöfer et al. 2002). Several measures have been reviewed in relation to mania including cerebrospinal fluid, post mortem, platelet, neuroendocrine challenge, and tryptophan depletion studies and they provided some evidence to support the hypothesis that a 5-HT deficit is involved in mania (Shiah and Yatham 2000).

Kynurenic acid (KYN) controls the neurotransmission of glutamine and dopamine and elevated brain KYN appears to be related to psychotic symptoms and cognitive impairment (Erhardt et al. 2017). Relative to controls, patients with BD have shown decreased neuroprotective kynurenine metabolites in the hippocampus and amygdala (Savitz et al. 2015). Whilst these all provide interesting hypotheses, there is as yet no definitive understanding of the chemical pathways involved in mania.

1.1.6 Findings from brain activation and brain imaging

In a word-generation task, decreased right rostral and orbital prefrontal cortex activation and decreased orbitofrontal activity during rest were associated with mania (Blumberg 1999). In a functional MRI (fMRI) study comparing manic patients (n=9) to healthy controls (HC) (n=9) on a facial recognition task it was found that manic patients had significantly increased activation in the left amygdala and reduced bilateral activation in the lateral orbitofrontal cortex relative to HC (Altshuler, Bookheimer et al. 2005). On the Go-NoGo task, mania was associated with significant reduction of task-related activation of right lateral orbitofrontal function, which may aid in explaining some disinhibition seen in mania. In addition, it was found that hippocampal and cingulate activation were decreased (Altshuler, Bookheimer et al. 2005). Sigitova et al (2017) summarized recent fMRI evidence which showed that the affective

symptoms of BD may be associated with brain regions involved in emotional regulation. They elaborated that these findings were consistent with overactivation of the amygdala, striatum and thalamus.

MRI studies have been reviewed to identify neuroanatomical risk factors for BD. Hajek et al. found that possible candidates for risk factors for BD are volumetric abnormalities of the subgenual prefrontal cortex, striatum, white matter, and possibly the hippocampus and amygdala (Hajek, Carrey et al. 2005). Brambilla et al. found significantly larger left amygdala volumes in BD compared with HC (Brambilla 2003). Sub–cortical volume analysis revealed consistent volumetric reductions in BD in the hippocampus and thalamus and enlarged lateral ventricles. In addition, cortical grey matter was thinner in frontal, temporal and parietal regions of both brain hemispheres. BD had large general effects on mean grey matter thickness in both left and right brain hemispheres (Andreassen 2017). Lopez-Larson et al. found that patients with BDI have subregion-specific grey matter volume reductions in the prefrontal cortex when compared to HC (López-Larson, DelBello et al. 2002). Another review noted that in BD, abnormalities in the third ventricle, frontal lobe, cerebellum, and possibly the temporal lobe are present (Beyer and Krishnan 2002). It has also been shown that patients with BD have an enlargement of the amygdala and possibly the thalamus and globus pallidus (Strakowski, DelBello et al. 1999).

Phillips and Swartz (2014) conducted a critical appraisal of neuroimaging studies of BD and conceptualized the disorder in terms of neural circuitry as one of parallel dysfunction in prefrontal cortical hippocampal-amygdala emotion-processing and emotion-regulation circuit bilaterally, along with an overactive left-sided ventral striatal-ventrolateral and orbitofrontal cortical reward-processing. Strakowski, DelBello and Aldler (2005) reviewed the functional neuroanatomy of BD and stated that the disorder involves dysfunction within subcortical (striatal-thalamic)-prefrontal networks and the associated limbic modulating

regions (amygdala, midline cerebellum). The authors further posited that the resulting dysregulation of mood in the disorder may be suggestive of diminished prefrontal modulation of subcortical and medial temporal structures within the anterior limbic network (amygdala, anterior striatum and thalamus). The aforementioned results are considered to relate to behavioural abnormalities that are core features of BD including emotional lability and dysregulation, and heightened reward sensitivity. Accompanying these are gray matter reductions in the prefrontal and temporal cortices, amygdala and hippocampus (Phillips and Swartz 2014).

Imaging studies of brain chemistry have reported that glutamine/glutamate ratio is significantly higher in the anterior cingulate cortex and parieto-occipital cortex in BD (Öngür, Jensen et al. 2008). Studies have consistently noted elevations in striatal choline concentration and reported decreased N-acetyl aspartate in prefrontal cortical regions of those with BD (Cerullo, Adler et al. 2009).

1.1.7 Comparison of bipolar disorder with reference conditions

One method to increase understanding of a disorder is to compare it with another disorder which shares similar features, for example schizophrenia (SZ). Flor-Henry proposed that manic-depressive and schizophrenia-like disturbances originated from the right and left temporal lobes respectively (Flor-Henry 1969). With advances in neuroimaging, some degree of laterality of BD and SZ has since been observed. Meta-analyses have shown that in BD, compared to healthy control (HC), a number of brain regions are affected including the medial temporal lobes (Yu, Cheung et al. 2010). In a meta-analysis of magnetic resonance imaging (MRI) studies in BD and SZ, BD was associated with smaller lateral ventricular volume and enlarged amygdala volume (Arnone, Cavanagh et al. 2009). Other smaller studies have found differing results. In an MRI study of temporal lobe structures in males with BD or SZ it was shown that hippocampal volumes were significantly smaller in the SZ group than in both BD

and HC. In addition, amygdala volumes were significantly larger in the BD group than in both SZ and HC participant groups (Altshuler, Bartzokis et al. 2000). In a different study of cerebral asymmetry in BD versus SZ, it was found that the left amygdala was smaller and the right anterior superior temporal gyrus was larger in BD but not SZ (Pearlson 1997). These show differing results affecting the temporal lobes in BD.

BD has also been compared with major depressive disorder (MDD) on volumetric neuroimaging. It has been found that whole brain volumes of patients with mood disorders do not differ from those of HC. Regional deficits in the frontal lobe, particularly in the anterior cingulate and the orbitofrontal cortex, differentiate participants with MDD or BD from HC (Konarski, McIntyre et al. 2008). In a recent review comparing patterns of volume alteration in MDD and BD it was demonstrated that both disorders were associated with lower grey-matter volume relative to HC in a number of areas. Conjunction analysis showed smaller volumes in both disorders in clusters in the dorsomedial and ventromedial prefrontal cortex, including the anterior cingulate cortex and bilateral insula. Group comparisons indicated that findings of smaller grey-matter volumes relative to HC in the right dorsolateral prefrontal cortex and left hippocampus, along with cerebellar, temporal and parietal regions were more substantial in MDD. These results suggest that MDD and BD are characterised by both common and distinct patterns of grey-matter volume changes (Wise 2017).

1.2 Mania and temporal lobe epilepsy

An alternative method to increase understanding of mania is to compare BD with another disorder which has localizing brain pathology, in this instance focal epilepsy arising from the temporal lobes (FS). The temporal lobes are one of the four major lobes in the mammalian brain along with the frontal, parietal and occipital lobes. The following overview of TLE builds the case for its use as a reference condition which is then taken up in the succeeding chapters 2-5 based on published research papers investigating the extent of association between the two

conditions with respect to precipitants, cognition, treatment and substance use. These papers are introduced in the final section, 1.3, of the present chapter.

Humans with amnesia and animal models of amnesia in the primate brain have allowed scientists to better understand the anatomical components of the brain for memory, that is the medial temporal lobe (Squire and Zola-Morgan 1991). The medial temporal lobe includes a system of structures that are crucial for declarative memory (conscious memory for facts and events). This consists of the hippocampal region (CA fields, dentate gyrus, and subicular complex) and the adjacent perirhinal, entorhinal, and parahippocampal cortices (Squire, Stark et al. 2004). One example of declarative memory is recognition which is the ability to judge a recently encountered item as having been previously presented (Squire, Wixted et al. 2007). Experiential phenomena may occur with spontaneous seizures or evoked by brain stimulation. Experiential phenomena most often encompass perceptual, mnemonic and affective features, in combination or in isolation, and commonly relate to the patient's individual past experience (Gloor 1990).

1.2.1 Temporal lobe epilepsy and seizures

Focal seizure (FS) includes both simple partial and complex partial seizures (PS). Where the focal seizure arises from the temporal lobe the term is synonymous with temporal lobe epilepsy (TLE) in the International League Against Epilepsy (ILAE) classification (Berg, Berkovic et al. 2010). In 2017, the ILAE published a position paper of the commission for classification and terminology and the following changes were made: (1) “partial” becomes “focal”; (2) awareness is used as a classifier of focal seizures; (3) the terms dyscognitive, simple partial, complex partial, psychic, and secondarily generalized are eliminated (Scheffer, Berkovic et al. 2017).

In this thesis, the change in nomenclature from PS to FS to TLE reflects the ever-changing landscape that is used to describe epilepsy syndromes, and accordingly the term used,

depends on the most current usage in the literature being reviewed. The term epilepsy reflects a diagnostic umbrella encompassing a variety of neurological disorders. Fisher et al. and the ILAE put forth several definitions: “Epilepsy is characterised by an enduring predisposition to generate seizures and the neurological, cognitive, psychological and social consequences that ensue.” The ILAE defined an epileptic seizure as: “A transient occurrence of signs and/or symptoms due to abnormal, excessive or synchronous neuronal activity in the brain.”

The effects of seizures can include alterations in sensory, motor, autonomic function, consciousness, emotional state, memory, cognition or behaviour. Common symptoms include staring, unusual feelings, twitching, a loss of consciousness and jerking of the peripheral limbs (Fisher, Boas et al. 2005).

Types of seizures include symptomatic seizures (identifiable brain disease), further classified as acute (resulting from active brain disease) or remote (which involve static brain insults). Generalised seizures (including absence, atonic, tonic-clonic, tonic, myoclonic), simple partial/focal seizures (where consciousness is maintained), complex partial seizures (where altered consciousness occurs), non-epileptic and status epilepticus (partial, complex partial or generalised) (Reddy, 2013). Diagnosis is based on neurological history and examination including obtaining eyewitness description of seizures, EEG, MRI and positron emissions tomography (PET) (Engel 2001).

Medial/Mesial Temporal Lobe Epilepsy (MTLE) is the most common form of epilepsy in adults (Cohen-Gadol, Bradley et al. 2005). Epileptogenic regions of the brain include the hippocampus, amygdala, perihippocampal and entorhinal cortex (Bernasconi, Bernasconi et al. 2003). Typically, the age of onset is in adolescence or early adulthood although a history of complicated febrile seizures, head trauma or infection within the first 4 or 5 years of life is usually present (Mathern, Pretorius et al. 1995). TLE typically originates from one medial

temporal lobe (Travers 1991). Due to the localizing pathology of TLE we may better understand mania and BD (in Chapter 3 and 4) when comparing the two disorders.

1.2.2 Similarities between bipolar disorder and epilepsy

In patients with epilepsy, up to 30% will experience some sort of psychiatric comorbidity (Vuilleumier and Jallon 1998). These include mania, depression, anxiety, psychoses, cognitive disorders, suicidal ideation and attempts (Hermann, Seidenberg et al. 2008). These can present during the prodromal, ictal (which refers to the actual seizure), post-ictal or inter-ictal phases (Gaitatzis, Trimble et al. 2004). Behavioural manifestations of seizures and misinterpretations of symptoms can complicate psychiatric assessments in patients with epilepsy (Mula, Schmitz et al. 2008).

Both BD and epilepsy constitute striking manifestations of brain disorders. Speculation has included the extent to which these two superficially very different disorders share common aetiology, pathogenesis and treatment responses. Similarities between BD and epilepsy include their episodic and often chronic clinical course, the observed efficacy of antiepileptic medications, and proposed involvement of kindling mechanisms (Mula, Marotta et al. 2010).

Kindling was originally proposed as contributing to the pathogenesis of epilepsy based on research in animals whereby repeated administration of an electrical stimulus results in the culmination of a generalized seizure (Girgis 1981). In BD, Post (1992) posited that external stressors and episodes may leave residual traces and vulnerabilities to further occurrences of affective illness. At the physiological level, permanent alterations in neuronal activity arise when long-term multiple central nervous system challenges occur following repeated episodes of affective illness (Berk et al. 2011). Shapero et al. (2017) examined early life adversity, proximal life events and the occurrence of affective episodes in BD (n=145). Early childhood adversity sensitised participants to the effects of recent stressors for depressive but not for hypomanic episodes. Stressful life events were associated with the initial rather than later

affective episodes in BD (n= 149) (Subramanian et al. 2017). In BDII (n=102) however the number of past episodes was not influenced by the relationship between life events and time onset of mood episodes (Weiss et al. 2015). A review of life stress and kindling in BD, found that 1 in 3 retrospective studies in humans supported the involvement of kindling mechanisms (Bender and Alloy 2011).

1.2.3 Treatment overlaps between BD and epilepsy

Antiepileptic drugs (AEDs) are used in both BD and epilepsy. Randomized controlled trials (RCT) have shown that carbamazepine, oxcarbazepine, lamotrigine and valproate are effective in BD (Muzina, El-Sayegh et al. 2002). The delayed clinical efficacy of AEDs in BD is indicative that the pathophysiological mechanisms may be distinct from those that are relevant to epilepsy, pain syndromes and neuromuscular disorders (Rogawski and Löscher 2004). The mechanism of action of lithium in preventing recurrences of illness episodes is only partially understood (Alda 2016). One proposed mechanism of the efficacy of lithium is related to the depletion of inositol by inhibition of the enzymatic breakdown of inositol phosphates to free inositol. The resulting reduction of free intracellular inositol is thought to slow the recycling of inositol containing metabolites required for signal transduction. In some animal models, low doses serotonin and dopamine are protective against limbic seizures and in high concentrations exhibit proconvulsive properties (Amann and Grunze 2005). Similar to lithium, the mood-stabilizing action of VPA and carbamazepine have been linked to inositol depletion (Berridge, Downes et al. 1989). It has been recognized that AEDS have a deleterious effect on mood, including depression which is reported in a number of patients taking drugs including barbiturates, vigabatrin and topiramate (Mula and Sander 2007). AEDS have been associated with mania with almost all drugs except valproate, lamotrigine, and levetiracetam (Mula and Monaco 2006).

1.2.4 Prevalence ratio of BD in epilepsy

The similarities between the two extend to their episodic manifestations. Mania and TLE share psychopathological symptoms including sensory, perceptual, cognitive and affective changes (Silberman, Post et al. 1985). Not only do the two disorders share common features, they can also co-occur. The prevalence ratio for diagnosed BD in epilepsy is 2.11% (95% CI 1.82-2.45) (Ottman, Lipton et al. 2011). Mania is more common in patients with TLE than in the general population (Lyketsos, Stoline et al. 1993) and symptoms of BD are often found in patients with epilepsy (Lyketsos, Stoline et al. 1993, Ettinger, Reed et al. 2005). In a study on the prevalence of BD in epilepsy, it was shown that 11.8% of patients had the DSM-based diagnosis of BD, whereas only 1.4% of participants were thought to have ‘‘pure” BD. This was attributed to the observation that in all other cases BD symptoms were related to phenotype copies of BD such as inter-ictal dysphoric disorder of epilepsy, postictal manic or hypomanic states, and pre-ictal dysphoria (Mula, Schmitz et al. 2008).

1.3 Research publications investigating similarities between mania and TLE

This section introduces the series of four published review papers presented in chapters 2 to 5. The first paper investigates the extent of overlap between mania and TLE with respect to precipitating factors, the second paper compares inter-episode neuropsychological deficits in bipolar disorder and TLE. The third paper examines the clinical application in mental disorders of an evidence-based treatment used in refractory epilepsy treatment, the ketogenic diet. The fourth focusses on an aspect of the precipitants of mania, that of reported substance-induced mania secondary to the consumption of herbal medicines.

1.3.1 Comparison of precipitating factors for mania and partial seizures

Chapter 2 presents a published paper that reviews precipitating factors of recurrent episodes of mania and partial seizures. *Bostock ECS, Kirkby KC, Garry MI & Taylor BVM (2015). A comparison of precipitating factors for mania and partial seizures: indicative of shared pathophysiology? Journal of Affective Disorders, 183, 57-67.*

Comparing and contrasting precipitating factors between two disorders which share common features may be a fruitful line of research. Several studies have taken this approach in the fields of psychiatry and neurology. In the Iowa 500 study, the precipitating factors of schizophrenia and primary affective disorders (Clancy, Crowe et al. 1973) were compared to assist in delineating the two syndromes. Precipitating factors have also been reviewed as a component of a comparison between migraine and epilepsy (Haut, Bigal et al. 2006). The examination of precipitating factors that are temporally linked to illness episodes may inform research into underlying neurobiological mechanisms involved in the occurrence of episodes. Precipitating factors may enhance our understanding of the causes of mania.

This paper addresses the following research questions:

- What are the precipitating factors in bipolar disorder and partial seizures arising from the temporal lobes?
- Are there common precipitating factors in the two disorders?
- What brain mechanisms have been imputed to account for the action of these common precipitating factors?

1.3.2 Cognitive function in euthymic BD-I and pre-surgical TLE

Chapter 3 presents a published paper comprising a systematic review of cognitive function in euthymic BD-I and pre-surgical TLE: *Bostock, ECS, Kirkby KC, Garry MI & Taylor BVM. (2017). Systematic review of cognitive function in euthymic bipolar disorder and pre-surgical temporal lobe epilepsy. Front. Psychiatry, doi: 10.3389/fpsyt.2017.00133.* This paper compared the inter-episode deficits in order to better understand trait markers of both disorders. Further research involving a head-to-head comparison of the two disorders on a broad range of neuropsychological tests is needed to clarify the nature and extent of cognitive deficits and potential overlaps.

This paper addresses the following research questions:

- What neuropsychological deficits have been identified in bipolar disorder and temporal lobe epilepsy?
- Are there common neuropsychological deficits in the two disorders?
- What brain mechanisms have been imputed to account for the action of these common neuropsychological deficits?

1.3.3 The ketogenic diet (KD) as a treatment in mental disorders

Chapter 4 presents a published paper regarding the status of the ketogenic diet (KD) as a treatment in mental disorders: *Bostock ECS, Kirkby KC and Taylor BVM (2017) The Current Status of the Ketogenic Diet in Psychiatry. Front. Psychiatry 8:43. doi: 10.3389/fpsyt.2017.00043.* The aim of this review paper is to clarify the potential role of KD in a variety of psychiatric conditions including; anxiety, depression, bipolar disorder, schizophrenia, autism spectrum disorder and attention deficit hyperactivity disorder. The methodology consisted of a review of electronic databases which included PubMED, PsychINFO and Scopus.

This paper addresses the following research questions:

- To what extent has the ketogenic diet been used in psychiatric conditions or animal analogues?
- What is the current evidence of the efficacy of the ketogenic diet in psychiatry?

1.3.4 Mania associated with herbal medicines

Chapter 5 presents a published paper examining substance-induced mania, in this instance associated with use of herbal medicines (HM). *Bostock ECS, Kirkby KC, Garry MI, Taylor BV and Hawrelak JA (2018) Mania associated with herbal medicines, other than cannabis: a systematic review and quality assessment of case reports.* This systematic review examines published reports linking mania with the consumption of HM. A comprehensive search of the

electronic databases EMBASE, CINAHL, Health Source, PsychINFO and PubMed was conducted.

This paper addresses the following research questions:

- Which herbal medicines have been associated with mania? Does the association confirm causality?
- What mechanisms have been imputed to explain the association?

Chapter 2

A comparison of precipitating factors for mania and partial seizures: indicative of shared pathophysiology?

This chapter contains the first of four publications in the thesis:
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Review

Comparison of precipitating factors for mania and partial seizures: Indicative of shared pathophysiology?

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ABSTRACT

Objectives: Mania in bipolar disorder (BD) and partial (focal) seizures (PS) arising from the temporal lobes, have a number of similarities. Typically, a chronic course of the disorders is punctuated by acute illness episodes. Common features of episodes may include sensory, perceptual, cognitive and affective changes. Both respond to anticonvulsant treatment. Common mechanisms imputed include neurotransmitters and kindling processes. Further investigation may improve understanding of the occurrence of both mania and PS, casting light on the relevance of temporal lobe mediated processes and pathology. One avenue of investigation is to compare aetiological factors and determine the extent of overlap which may indicate shared brain localization or pathophysiology. Aetiology includes predisposing, precipitating or perpetuating factors. This paper examines the literature on precipitating factors of mania, first or subsequent episode, and of PS in diagnosed epilepsy, which is the second or subsequent seizure, to identify the extent and nature of their overlap.
Method: Narrative review based on a literature search of PubMed and Google Scholar.
Results: Precipitating factors for both mania and PS were stress, sleep deprivation, antidepressant medication and, tentatively, emotion. For mania alone, goal-attainment events, spring and summer season, postpartum, and drugs include steroids and stimulants. For PS alone, winter season, menstruation and specific triggers in complex reflex epilepsies. Those not substantiated include lunar phase and menopause. A wide range of chemicals may provoke isolated seizures but by definition epilepsy requires at least two seizures.
Conclusions: The overlap of precipitating factors in mania and PS imply that common brain processes may contribute to both, consistent with findings from neuroscience research.

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1. Introduction

The precise pathogenesis of bipolar disorder (BD) is unknown, though it is generally agreed that its development is influenced by genetic and environmental factors (Craddock and Jones. 1999). Currently there are no biological markers available for a definitive diagnosis of BD, rather diagnosis is based on signs and symptoms. The cardinal feature of BD type I (BDI) is mania, characterized by "a distinct period of abnormally and persistently elevated, expansive, or irritable mood, lasting at least 1 week (or any duration if hospitalization is necessary)" (American Psychiatric Association, 2013). Episodes of mania may lead to marked impairments in social and occupational functioning and impose a significant financial burden on both patient and health care system. In order to alleviate this burden a more detailed understanding of the aetiology and pathogenesis of mania is important to direct development of improved treatments.

Aetiology is commonly classified in terms of predisposing, precipitating and perpetuating factors, all of which are highly relevant to understanding the onset and course of a disorder. This review considers one of these dimensions, precipitating factors, which consist of recurrences of episodes in established cases of illnesses distinct from the cause of an initial episode. Two reviews have focused on the precipitating factors of mania/ hypomania in young adults (Proudfoot et al., 2012) and adults (Proudfoot et al., 2011). The examination of precipitating factors that are temporally linked to illness episodes may inform research into underlying neurobiological mechanisms involved in the occurrence of episodes.

Further insights may be gained by comparing and contrasting precipitating factors between two disorders which share common features. Several studies have taken this approach in the fields of psychiatry and neurology. In the Iowa 500 study, the precipitating factors of schizophrenia and primary affective disorders (Clancy et al., 1973) were compared to assist in delineating the two syndromes. Precipitating factors have also been reviewed as a component of a comparison between migraine and epilepsy (Haut et al., 2006). Following this approach, a potential reference condition for comparison with mania is partial seizures arising from the temporal lobes. The term partial seizures (PS) includes both simple partial and complex partial seizures and is synonymous with focal seizures in the International League Against Epilepsy (ILAE) classification (Berg et al., 2010).

Both BD and epilepsy constitute striking manifestations of brain disorders. Speculation has included the extent to which these two superficially very different disorders share common aetiology, pathogenesis and treatment responses. The two disorders have long been of interest to the medical profession. In particular, the unusual behavioural disturbances rather than convulsions that may occur in epilepsy have been of interest since ancient times, reaching a peak in 19th century medical literature (Schmitz and Trimble, 1992). Renewed interest came with the advent of the electroencephalogram (EEG) and the discovery of forced normalization, a process which involves, in patients with epilepsy, the normalization of EEG recordings during psychotic states (Krishnamoorthy and Trimble, 1999). The then presumed beneficial relationship between epilepsy and psychosis resulted in the introduction of convulsive therapy as a treatment for psychosis (Sachdev, 1998).

Further, it was observed that the nature of the psychotic disturbance bore some relationship to the laterality of the epileptic focus. Flor-Henry (1969) proposed that manic-depressive and schizophrenia-like disturbances originated from the right and left temporal lobes respectively. With advances in neuroimaging, some degree of laterality of BD and schizophrenia has since been observed. Meta-analysis has shown that in patients with schizophrenia and bipolar disorder, compared to neurotypical control participants, gray matter volume is lower in the prefrontal cortex, thalamus, left caudate and medial temporal lobe and right insula. Schizophrenia has been associated with gray matter deficits in the left insula and amygdala (Yu et al., 2010). In epilepsy, PS typically originate from one medial temporal lobe, although they may be propagated from other structures which project to limbic areas (Travers, 1991). PS may be lesional or non-lesional and can be idiopathic or secondary, referring to the predisposing aetiology; all of these are included in this review which focuses on the precipitating factors for PS in established epilepsy.

Other similarities between BD and epilepsy include their episodic and often chronic clinical course, proposed involvement of kindling mechanisms and the observed efficacy of antiepileptic medications (Mula et al., 2010). In both disorders, kindling mechanisms may be involved in perpetuating illness episodes. In order to understand human limbic epilepsies, experimental kindling has been performed in rodents. This involves the observation of progressive changes that result from repeated electrical stimulation (Goddard et al., 1969). The premise that *seizures beget seizures* has long been postulated and in BD it has been hypothesised that stressors and relapses leave traces and cause vulnerabilities for future recurrences (Post, 1992). Mazza et al. (2007) provide a comprehensive explanation of the kindling paradigm with respect to BD and epilepsy.

The similarities between the two extend to their episodic manifestations. Mania and PS share psychopathological symptoms including sensory, perceptual, cognitive and affective changes (Silberman et al., 1985). Not only do the two disorders share common features, they can also co-occur. The prevalence ratio for diagnosed BD in epilepsy is 2.11% (95% CI 1.82–2.45) (Ottman et al., 2011). In a recent study in a sub-Saharan African population it was demonstrated that epilepsy occurs at a higher rate among first-degree relatives of patients with BD 15.2% than controls 2% and the rate of BD among those with epilepsy 14.5% compared with controls 2.1% (Jidda et al., 2014). In a population-based registry study, the proportion of BD among people with epilepsy was twice as high relative to individuals without epilepsy (Bakken et al., 2014). Mania is more common in patients with TLE than in the general population (Lyketsos et al., 1993) and symptoms of BD are often found in patients with epilepsy (Ettinger et al., 2005).

Seemingly unprovoked episodes may cause marked distress and impairments in social, occupational and financial wellbeing. By contrast, an increased understanding of episode precipitating factors can aid patients to have a sense of control over their illness and practitioners to formulate individual treatment plans. Given the similarities between BD and epilepsy, in particular PS arising from the temporal lobes, it may be expected that the two share precipitating factors. Precipitating factors refer to the catalyst for an illness, symptom or episode, distinguishing it from the underlying cause of an illness (Mosby, 2012). Precipitating factors may not be reliable predictors but are associated with an increased risk of an episode and are not usually deterministic. Several procedures may be used for provocation of epileptiform discharges, including hyperventilation, sleep deprivation and photic stimulation (Flink et al., 2002). In some instances, classification of epilepsy syndrome is based on precipitating factor, for example thinking, music and reading epilepsies (Engel, 2001).

Given the degree of interest in the relationship between bipolar disorder and epilepsy and the observed similarities between mania and PS in illness course, symptomatology and treatment response this review examines the precipitating factors in the two conditions. The extent of overlap of precipitating factors in both conditions is summarised as a pointer to potential shared localisation in the brain and pathogenesis. Suggestions are made for future research following these leads.

2. Methods

A review of the literature was conducted in August 2014, based on searches in PubMED and Google Scholar using the terms “bipolar disorder”, “manic depression” “epilepsy”, “temporal lobe epilepsy”, “precip*”, “precipitating factors”, “triggers”, “mania” “seizures” “complex” “partial” and each of the precipitating factors examined throughout the review. A hand-search of the reference lists of published articles was also conducted. Publications were included based on relevance and overall quality judged by the authors, with no restriction on year of publication. An initial literature search was conducted as per the search criteria listed above, abstracts of these studies were reviewed by authors EB and KK and in cases where their applicability to the subject area was questionable the full text article was examined and articles not relevant to the subject were discarded. For example, studies of precipitants in animal models and epidemiological studies which mentioned precipitating factors in passing but did not present data on the subject. All authors commented on the relevance of the remaining citations in their area of expertise.

For the purpose of reliability, similar to Proudfoot et al. (2011), only precipitating factors that (1) result in mania or hypomania in bipolar I or II disorder are included (2) secondary manias, due to drugs other than antidepressants, metabolic disturbances, infections, tumours and epilepsy are excluded although some other precipitating factors which are mentioned may be classed as secondary to drug use. In addition, this review focuses on (3) PS arising from the temporal lobes or (4) where data is unavailable, seizures of any type in established cases of epilepsy. Consistent with the cited literature, PS arising from the temporal lobes is referred to as temporal lobe epilepsy (TLE) where this is the original term used.

3. Results

The search strategy identified 126 articles that discussed precipitants of mania or temporal lobe epilepsy, that is factors with a close temporal relationship to a recurrence of illness and 39 relevant to candidate mechanisms of precipitants and these were included in the review.

3.1. Precipitating factors

This review compares precipitating factors for mania and partial seizures. Those evaluated are stress, goal-attainment events, emotion, sleep reduction, lunar phase, seasonal variations, reproductive life cycle stages, antidepressant medication and other precipitants.

3.2. Stress

The subjective definitions of stress and the use of ambiguous concepts such as stressful life events can result in the confusion of prodromal or episode symptoms in BD as well as in other conditions (Johnson and Roberts, 1995). Proudfoot et al. (2011) reviewed the impact of stressful life events on the onset of manic episodes and identified several retrospective studies which supported their role as a precipitating factor (Kennedy et al., 1983; Ambelas, 1987; Joffe et al., 1989). Major life events including death or suicide of a family member, divorce, unemployment and/or disability were associated with an increased risk of first admission with mania. Data were obtained from 17 years of hospital admissions for a total of 1556 patients. An acknowledged shortcoming of the study was that life events may have occurred as a consequence of symptomatic BD rather than a cause of admission for mania (Kessing et al., 2004).

A prospective study examined the effects of stressors on first episode and recurrent mania over three years (Gilman et al., 2014). Relapses of mania were more likely in participants who had experienced recent personal loss, interpersonal or economic difficulties, or past childhood maltreatment and abuse. In a two-year prospective study of 62 patients with BD 19% of relapses occurred after a significant/stressful life event in the month prior (Hunt et al., 1992). Following a common stressor, a hurricane in that instance, BD patients attending a lithium clinic had significantly increased depressive and manic relapses, despite adequate lithium levels during and subsequent to the event (Aronson and Shukla, 1987). The likelihood of experiencing stress before the onset of mania decreases with the age of the patient (Hlastala et al., 2000). Using prospective methodology, 125 individuals with BDI were interviewed monthly for approximately 3 years. Stressful life events preceded depressive but not manic relapses (Johnson et al., 2008). Others have failed to find support for the role of stressful life events in recurrences of mania, suggesting their importance applies more to the onset of the disorder than relapses (McPherson et al., 1993). These results support stressful life events as a precipitating factor in first episode of mania.

Patients with epilepsy commonly report stress as a precipitating factor for seizures (Frucht et al., 2000; Haut et al., 2003, 2007; Nakken et al., 2005; Ferlisi and Shorvon, 2014; Wassenaar et al., 2014) and stress is associated with increased seizure frequency (Temkin and Davis, 1984; Neugebauer et al., 1994). In a tertiary-care facility ($n=400$), stress was the most widely (30%) identified precipitating factor across different types of epilepsy, although patients with TLE were the most affected (46%) (Frucht et al., 2000). In children with temporal, frontal, occipital and parietal epilepsies, 20–30% reported the effects of stress and no significant difference was found between epilepsy syndromes (Fang et al., 2008). A strong relationship exists between severe stressors experienced by a whole population (for example emergency evacuation and war) and seizure frequency in both adults and children (Swinkels et al., 1998; Bosnjak et al., 2002). These effects may possibly be due to missed medications and social rhythm disruptions. These results indicate that recurrences of episodes in both disorders are associated with stress.

3.3. Goal-attainment events

Individuals who hold higher life ambitions, as assessed by the hypomanic personality scale, are vulnerable to episodes of mania (Johnson and Carver, 2006). In a sample of university students with BDII or cyclothymia, hypomanic symptoms were associated with preparing for and completing exams (Nusslock et al., 2007). It is believed that episodes of inflated confidence and self-esteem coupled with high ambitions lead to excessive goal pursuit which can precipitate mania (Johnson, 2005). Actions that relate to goal attainment (e.g., acceptance into graduate school, getting married, getting a new job) have been proposed as a precipitating factor for mania. A prospective study of 43 participants with BDI found that goal-attainment events were associated with increased manic symptoms (Johnson et al., 2000), a finding which was later replicated in a larger sample ($n=125$) (Johnson et al., 2008). Individuals with BDI reported mania after achieving an important success and avoiding rewarding activities to prevent mania (Edge et al., 2013). This effect may be related to the regulation of the behavioural activation system, a motivational system which regulates reward-mediated behaviours and emotional homeostasis (Depue and Iacono, 1989). Goal-attainment events are a precipitating factor for mania, however to our knowledge there is no research examining goal-attainment events and seizure control in those with PS.

3.4. Emotion

The key symptoms of mania, irritability, distractibility and emotional lability appear to be associated with abnormalities in emotion processing including the intensity and regulation of mood (Phillips et al., 2003). Prospective research has been used to examine the association between positive emotion and the subsequent clinical course of BD. Feelings of joy and amusement increased and feelings of compassion decreased in mania (Gruber et al., 2009). In young adults with BD ($n=198$) falling in love was rated by participants as a precipitating factor for mania (Proudfoot et al., 2012). This may be related to a dysregulation of the behavioural activation system. Not only might intense emotion predict increased symptoms of mania but emotional hyper-reactivity is demonstrated during mania, measured by arousal and attribution of valence in response to images (M'Bailara et al., 2012). Lability and a more severe course of BD are found in patients whose relatives show high levels of expressed emotion. Levels of mania and depression were predicted by subjective distress to relatives' criticisms and emotional over-involvement (Miklowitz et al., 2005).

Jackson (1931), a forefather of epilepsy research, noted that intense emotions may precipitate seizures in vulnerable individuals. Excitement, worry, anger, feeling upset and anxiety are commonly reported as seizure precipitants in young adults with epilepsy (Cull et al., 1996). Patients with mesial TLE ($n=71$) identified feelings of nervousness, worry, anxiety and anger as seizure precipitants. This group also reported utilizing the inhibitory methods of concentrating, deep-breathing and changing thoughts to avoid seizures (Lunardi et al., 2011). This supports the use of behavioural interventions to minimise excessive emotion in patients with epilepsy (Boylan, 2001). Intense emotion is a tentative precipitant of mania and this is an area that would benefit from future research. It is a widely reported precipitating factor in PS.

3.5. Sleep reduction

The relationship between BD and sleep is multifaceted. Changes in sleep patterns serve as a marker for manic or depressive episodes. It is an aetiological agent, a predictor for future episodes, a therapeutic target and an indicator for treatment response (Plante and Winkelman, 2008). Patients with BDI retrospectively identify altered sleep patterns due to social rhythm disruption in recurrences of manic episodes (Malkoff-Schwartz et al., 2000). The sleep-wake cycles of 67 patients with BD was examined during a depressive episode, 7 patients switched to mania or hypomania following 40 h of sleep deprivation (Wehr et al., 1982). Other prospective studies have provided support for the role of sleep deprivation and sleep reduction and the onset of mania (Leibenluft et al., 1996; Colombo et al., 1999; Bauer et al., 2006). Mania is also associated with travel across time zones, more commonly in east-bound travellers, whilst depression is more common in west-bound travellers, an effect possibly mediated by the physiological "phase shift" changes that affect body temperature, sleep and melatonin production (Jauhar and Weller, 1982; Young, 1995).

Patients with TLE commonly report sleep reduction as a precipitant to seizures (Frucht et al., 2000; Sperling et al., 2008; Ferlisi and Shorvon, 2014; Wassenaar et al., 2014). Rajna and Veres (1993) examined seizures diaries, sleep duration and PS in 14 patients with TLE for a period of 4995 days. It was demonstrated that even decrements of 1.5 h from patients' mean sleep time resulted in an increase of seizures. Not only does sleep affect seizures, seizures also affect rapid eye movement (REM) sleep. In patients with PS of TLE, a reduction in the duration of REM sleep is observed particularly when a seizure occurred in the day prior (Bazil et al., 2000). Sleep reduction and experimental/therapeutic sleep deprivation is a shared precipitating factor for both mania and PS arising from the temporal lobes.

3.6. Lunar phase

Historically, the moon was relied upon as a primary source of night-time light and throughout antiquity, the belief persisted that changes in behaviour were more prevalent during the full moon (Raison et al., 1999). This view was reportedly still held among mental health professionals in the 1990s (Vance, 1995). Lunar phase was correlated with bed-occupancy rate but not specific psychiatric diagnosis in a 12-month hospitals admissions dataset (Tejedor et al., 2010). In a meta-analysis of 37 studies, phase of the moon accounted for less than 1% of variance in psychiatric hospital admissions, psychiatric disturbances, crisis calls, homicides and other criminal offences (Rotton and Kelly, 1985).

Lunar phase and seizures were unrelated in a prospective three-year study although a possible effect was observed on non-epileptic seizures (those that resemble seizures without supportive EEG results) (Benbadis et al., 2004). During the full moon, there was an increase in hospital admissions (Polychronopoulos et al., 2006) and a peak in episodes of status epilepticus was observed 3 days after a new moon (Rüegg et al., 2008). In healthy individuals, during a full moon, average sleep time decreases by 20 min per night and morning fatigue increases compared to other lunar phases (Roosli et al., 2006). Taken together, these results suggest that the lunar phase exerts minimal influence on behaviour and seizure frequency mainly due to disruptions in sleep.

3.7. Seasonal variations

Seasonal variations have been widely examined as a precipitating factor for mania. Using hospital admissions data, increases have been found in summer (Takei et al., 1992; Barbini et al., 1995), and spring and summer (Mulder et al., 1990; Lee et al., 2002). By contrast, data obtained from Brazil has shown that a peak in instances of mania is observed during winter–spring months which is associated with the dryer, colder, increased daylight seasons (Volpe and Del Porto, 2006; Volpe et al., 2010). Some have found no effect of seasonality and hospital admissions for mania (Daniels et al., 2000).

Seasonal variations have been cited as a precipitating factor for seizures (Spatt et al., 1998). A study conducted over 2 years examined changes in weather and twice-monthly EEG recordings from 30 participants with epilepsy (Motta et al., 2011). Epileptiform discharges were more common in winter during unstable weather conditions and seizures most frequently occurred during spring, autumn and winter. Data obtained from seizure diaries has suggested that seizures are more frequent in winter (Clemens et al., 2013). This finding has been confirmed from data obtained from an inpatient facility where PS were less likely to occur on bright sunny days (Baxendale, 2009). These results suggest that instances of mania are related to seasonal effects with the strongest mediation by an increase in light, a finding which is in contrast to that of PS. It is worth noting that the effects of seasonality on mania have received far more attention in the empirical literature than in epilepsy with only one study cited examining the effects on PS.

3.8. Puberty/menarche

The effects on menarche on the onset of BD have been examined utilizing retrospective methodology. Fifty participants with BD were surveyed and 32% related the onset of the disorder to the period prior and 18% within one year of menarche whilst 20% reported the age of onset as 12 or younger and 6% later in life (Freeman et al., 2002), consistent with the typical age of onset between 15 and 25 years (Kessler et al., 2005).

The age of onset of mesial TLE is typically in adolescence or early life (Desgent et al., 2012). Contradictory findings on the effects of menarche on seizures have been observed. A longitudinal study spanning 7 years followed 39 patients with epilepsy (24 female, 15 male) during puberty. Eighty-seven percent of participants had the same number of seizures as in prepuberty. In female participants, better seizure control was obtained following menarche with a reduction of PS (Diamantopoulos and Crumrine, 1986). Others have noticed a worsening of symptoms at the time of puberty or menarche (Morrell et al., 1998). These results suggest that puberty or menarche may be important in the initial onset of BD but may have less of an effect in PS arising from the temporal lobe.

3.9. Menstruation

A recent review has examined the effects of the menstrual cycle on the course of BD, finding that it is likely affected with depressive and manic relapses occurring (Teatero et al., 2014). Interviews of women with BD have shown that two-thirds reported menstrual cycle symptom fluctuations, although the direction of the change to depression or mania was unclear due to retrospective methodology (Blehar et al., 1998; Rasgon et al., 2003). Another study examined mood of patients with BD 7 days prior to the onset of menses and 7 days after; mood changes were found in 11 of 25 participants although no consistent pattern of change was found (Leibenluft et al., 1999). This has also been found in a larger sample ($n=41$) (Shivakumar et al., 2008). A case study reported two women who experienced recurrent hyperactivity, a decreased need for sleep and irritability five days prior to menses, each of which are key features of mania. Euthymia was observed for the rest of their menstrual cycles and the women were successfully treated with lithium (D'Mello et al., 1993). Whilst these studies suggest that the menstrual cycle does affect symptoms there is no clear evidence to suggest that it is a precipitating factor in mania.

Seizure clusters that occur in relation to the menstrual cycle, known as catamenial epilepsy, is observed in approximately 12% of patients (Duncan et al., 1993). Patients with TLE are particularly vulnerable to the effects of menstruation. One study examined seizure precipitants across different types of epilepsy and found that 28% of patients with TLE cited menstruation as a precipitating factor, a proportion that was twice that of other epilepsy syndromes (Frucht et al., 2000). In addition, patients with mesial TLE also report the effects of menstruation on seizure exacerbations (Lunardi et al., 2011). An association between laterality of epileptic focus and catamenial epilepsy has been demonstrated. In a sample of 100 women with epilepsy those with left-sided TLE had seizures which peaked cyclically with the onset of menses (Quigg et al., 2009). Menstruation is a known precipitating factor for PS but its role in mania is still unclear.

3.10. Postpartum

Twenty-six percent (81 of 313 deliveries) of women with BDI or schizoaffective disorder experience postpartum psychosis (mania inclusive) (Jones and Craddock, 2001), which typically presents in the first two weeks following delivery of a child (Dean et al., 1989). Postpartum psychosis is associated with a longer duration of labour and night time delivery suggestive of the role of sleep in its onset (Sharma, 2004). Some have associated the birth of a child and mania in men (Davenport and Adland, 1982; Ambelas, 1987) although others have not supported this finding (Hunt and Silverstone, 1995).

The occurrence of seizures and/or coma during pregnancy or the postpartum period is known as eclampsia (Kaplan, 1999). In a sample of 26 presurgical patients with partial seizures and hippocampal sclerosis, eclampsia was identified as a possible risk factor for the development of the disorder and 30% related its onset to an eclamptic pregnancy (Lawn et al., 2004). The postpartum period is a precipitating factor for mania and is a possible risk factor for the development of PS arising from the temporal lobes.

3.11. Perimenopause/menopause

Freeman et al. interviewed 50 women with BD and according to self-report, 9 were perimenopausal and 13 postmenopausal. Three participants reported that the onset of BDI occurred during or after perimenopause. Half of the participants reported mood worsening associated with perimenopause, including irritability ($n=8$), more rapid cycling ($n=6$) and hypomania or mania ($n=8$) (Freeman et al., 2002). The self-reported perimenopausal worsening of symptoms including mania, hypomania and depression has been replicated (Blackmore et al., 2008). Wehr et al. (1988) interviewed participants with BD and demonstrated that of those whose illness had a rapid cycling course ($n=47$) almost 50% reported that their illness became rapid cycling ($n=9$) or persisted ($n=14$) following menopause. In another study of 56 postmenopausal women with BDI, almost 20% of participants reported experiencing emotional problems associated with menopause, including manic episodes, anxiety, agitation and depression. One participant interviewed received a diagnosis of BD at the time of menopause subsequent to a manic episode (Blehar et al., 1998).

During the perimenopausal period, an increased risk for new onset seizures or the worsening of seizures occurs. Conversely during menopause, improvements were seen in patients whose seizures had previously followed a catamenial pattern (Rościszewska, 1977). This was also observed in patients with TLE (Harden et al., 1999). Menopause may also constitute a risk factor for epilepsy with one study finding that some women had new onset seizures during this period (Abbasi et al., 1999). In contrast with Harden et al. these authors found a lower seizure frequency in perimenopausal women compared to the pre and post menopausal women, but they did not differentiate epileptic focus. During the perimenopausal period, an

elevation of the estrogen to progesterone ratio occurs (Santoro et al., 1996) and even in healthy women this period is associated with changes in mood, possibly mediated by disruptions in sleep (Baker et al., 1997). In summary the effects of perimenopause and menopause on mania and PS are uncertain due to methodological limitations of research largely based on retrospective self-report without hormone level verification.

3.12. Antidepressant medication

The use of antidepressant medication carries the risk of switch to mania. Antidepressant-associated mood switching has been found in BD (Ghaemi et al., 2004; Schneck et al., 2008). The switch has been found with the use of selective serotonin reuptake inhibitors (SSRIs) (Burrai et al., 1991), bupropion (Aggarwal and Sharma, 2011), monoamine oxidase inhibitors (MAOIs) (Stoll et al., 1994) and tricyclic antidepressants (Wehr and Goodwin, 1979). Mania has also been associated with the use of the herbal supplements Yohimbine which acts as a mild MAOI (Price et al., 1984) and St John's wort, which is reported to have antidepressant qualities and has SSRI activity (Moses and Mallinger, 2000). Wehr et al. (1988) demonstrated that, in those with rapid cycling BD ($n=51$), 37% showed remission or a slowing of symptoms following the discontinuation of antidepressant medication. The risk of antidepressant-induced mania was increased (95% CI = 1.12, 7.19, $p=0.028$) when patients with BD received monotherapy relative to those treated with an adjunct mood stabilizer. Data was obtained from 3240 patients (Viktorin et al., 2014). Some have cautioned against the use of antidepressants in BD reserving their use for acute cases, given the significant risk of mania and possible worsening of the illness (Ghaemi et al., 2003).

Approximately 30% of patients with epilepsy will experience some sort of psychiatric comorbidity with depressive disorders affecting between 20 and 60% of patients (Vuilleumier and Jallon, 1998). Depression appears to be related to epilepsy with a left-sided temporal lobe focus (Altshuler et al., 1990) and mesial temporal sclerosis (Quiske et al., 2000). Tricyclic antidepressants, buproprion (Peck et al., 1983), SSRIs (Prasher, 1993) Yohimbine and St John's wort have been associated with seizures in humans (Tyagi and Delanty, 2003). Due to the lowering of the seizure threshold and interactions with antiepileptic medication the use of antidepressant medication requires caution in this patient population. In sum, antidepressant medication is a precipitating factor in both disorders.

3.13. Other

There are a large array of precipitating factors for mania and PS and this review has included those that are more commonly reported by patients or described by clinicians. Cognition-induced epilepsy refers to a broad group of syndromes for which seizures are precipitated by specific cognitive tasks (e.g., playing chess or card games) (Ritaccio et al., 2002). These complex stimuli may involve emotional, motivational or mnestic components suggestive of the integration of complex stimuli within limbic structures (Sturm et al., 2002). To our knowledge, there are no such precipitants of mania. This may be due to the longer time interval between precipitant and episode in BD than in triggered epilepsies. Mania is not reported to be a reflex phenomenon to cognitive tasks.

Steroids, levodopa and dopaminergic agents, sympathomimetic amines, triazolobenzodiazepines, hallucinogens (Sultzer and Cummings, 1989), DHEA (Markowitz et al., 1999), chloroquine (Lovestone, 1991), metoclopramide (Ritchie and Preskorn, 1984), lupron (Rachman et al., 1999), varenicline (Alhatem and Black, 2009), the antimicrobials clarithromycin, isoniazid, erythromycin and amoxicillin (Ahmed et al., 2002), steroid nasal spray (Goldstein and Preskorn, 1989), energy drinks (Machado-Vieira et al., 2001) and caffeine (Ogawa and Ueki, 2003) have also been cited as precipitating factors for mania although many are case reports. There is a high prevalence of co-morbid alcohol misuse and BD which is associated with increased mood lability, impulsivity, violence and polydrug use (Salloum et al., 2002). Alcohol can precipitate seizures in patients with epilepsy (Heckmatt et al., 1990; Frucht et al., 2000). This is more commonly associated with chronic heavy use (Yamane and Katoh, 1981). The occurrence of mania or PS precipitated by a pharmaceutical or chemical agent reflects the interaction of underlying vulnerabilities and the drug and is strongly dependent on the dosing of the substance involved.

4. Discussion

The evidence reviewed is primarily derived from clinical observational or questionnaire studies in humans, epidemiology and animal studies. In particular sleep deprivation in rodents is used as an explanatory paradigm for mania, epilepsy and stimulus precipitants in animals, for example the use of electrical kindling as a model of partial epilepsy. This review compared the range of precipitating factors for mania and partial seizures arising from the temporal lobes. These factors were stress, goal-attainment events, emotion, sleep reduction and deprivation, lunar phase, seasonal variations, menstruation, the postpartum period, perimenopause/menopause and antidepressant medication. The precipitating factors common to mania and PS include stress, sleep reduction and deprivation, antidepressant medication and more tentatively emotion. Goal-attainment events, spring and summer season and the postpartum period were only associated with mania, whereas winter season and menstruation were only associated with PS. The identification of precipitating factors common to mania and PS is suggestive of overlaps in candidate mechanisms, in particular temporal lobe involvement in the generation of episodes in both disorders. These factors and postulated mechanisms of action are discussed in turn below.

The mechanisms by which stress can alter susceptibility for mania and PS are not well understood. They are believed to include many neural and endocrine pathways and a balance between those that promote seizures and those that protect against (Reddy and Rogawski, 2002). It is established that, early life stress and stress affect the medial temporal lobe (Herman et al., 2003) and the hypothalamic–pituitary–adrenal (HPA) axis (Phillips, 2007) and has been hypothesised to influence the development and progression of limbic epilepsy (Koe et al., 2009) and BD (Agid et al., 1999). HPA axis dysfunction has been found in patients with epilepsy (Zobel et al., 2004) and BD (Watson et al., 2004). It is likely that these deficits or insults caused earlier in life cause vulnerability for future episodes.

The effects of stress on mania and PS susceptibility may be modulated by the endocrinological response to stress. During periods of stress, the adrenal cortex releases corticotropin-releasing hormone (CRH), adrenocorticotropic hormone (ACTH) and cortisol (corticosterone in rodents) (Joëls, 2009). In animals, the administration of corticosteroids facilitates kindling in amygdala and the hippocampus (Karst et al., 1999) and exposure to repeated stress accelerates limbic epileptogensis (Jones et al., 2013). The administration of exogenous corticosteroids has been implicated in the onset and recurrence of mania (Pies, 1981; Panwar and Lassi, 2011). By contrast, in patients with Cushing's disease, marked by excessive endogenous secretion of cortisol, symptoms of increased fatigue, irritability and depressed mood are commonly reported (Starkman et al., 1981). Meta-analysis has shown that morning cortisol level is increased in BD patients relative to controls ($N=704$, $g=0.269$, 95% CI 0.084–0.453, $p=0.004$) (Girshkin et al., 2014).

The adrenal medulla responds to stress by producing the catecholamines epinephrine and norepinephrine. The effects of these are simulated by the analogues of epinephrine, pseudoephedrine (found in some cold and flu remedies) (Dalton, 1990; Stuer and Claes, 2006) and ephedra (found in some weight-loss supplements) which have been reported to precipitate mania (Lewis and Smith, 1983; Capwell, 1995). The finding that stress is a precipitating factor in the two disorders is suggestive of shared pathophysiology involved in the generation of episodes. Stress is also a precipitating factor in other neurological conditions characterized by recurrent attacks affecting the central nervous system, for example multiple sclerosis. Stress is often coupled with other known precipitating factors such as sleep reduction.

This review has shown that intense emotion can precipitate PS and more tentatively mania. Patients with mania show decreased recognition of fear and disgust compared to faces expressing anger, sadness, surprise and happiness (Lembke and Ketter, 2002). Patients with early-onset right mesial TLE show impaired recognition particularly for fearful faces (Meletti et al., 2003). In addition, impairments in matching facial emotional expressions are found in remitted patients with BD (Bozikas et al., 2006). These results are suggestive of the involvement of the limbic system in both disorders. Clarifying the role of intense emotion as a precipitating factor of mania would require careful attention to trait and state emotions as a feature of the disorder itself.

As indicated in the results, sleep reduction and deprivation are precipitating factors for mania and PS. In rats and mice, sleep deprivation leads to symptoms akin to mania in humans including insomnia, hyperactivity, irritability, aggressive behaviours and hyper sexuality (Benedetti et al., 2008). The importance of sleep reduction in the onset of mania has been acknowledged as a potential final common pathway. Mania is hypothesised to cause insomnia and its development is self-reinforcing and potentially autonomous after being initiated by precipitants such as psychological, environmental and interpersonal factors (Wehr et al., 1987). Sleep deprivation can elicit paroxysmal EEG activity in healthy individuals (Rodin et al., 1962) and is an important predictor of interictal epileptiform discharges, implicated in the onset of recurrent seizures (Mattson et al., 1965). A reduction in the seizure threshold has been observed following sleep deprivation in amygdala kindled cats (Shouse and Sterman, 1982). The influence of the circadian rhythm system on seizure frequency has been shown in animal models of limbic epilepsy and in humans with partial epilepsy with a prevalence of seizures occurring in the daytime with a peak in the afternoon (Quigg et al., 1998). Also noteworthy is that at times, the terms sleep deprivation is used synonymously with sleep reduction in particular in the epilepsy literature. Research on sleep hygiene in both disorders may cast further light on the mechanisms in the generation of episodes.

Sleep and the functioning of the circadian rhythm systems are influenced by external cues including the *Zeitgeber* light, the effects of which may be most prominent during seasonal variations or historically, with lunar phase. Humans are particularly sensitive to light which, through entrainment, is aligned with external time that allows a shift according to seasonal variation and changes in time zone (Harvey, 2008). Seasonal variations are a precipitating factor in both disorders although exacerbations of mania and PS are seen at different times of the year. In BD, there is a relationship between higher sunshine hours and increased incidence of mania (Carney et al., 1988). Heightened sensitivity to light has been proposed as a possible phenotype for BD (Lewy et al., 1985). Additionally, a recent multinational study has found an association between sunlight and age of onset and BD (Bauer et al., 2014). The relationship between light and mood extends beyond a precipitating factor to a treatment. Light therapy can be used as a treatment for depression. Side effects may include rapid mood swings (Meesters and Van Houwelingen, 1998) and case reports of mania occurring 5–6 days later (Schwitzer et al., 1990). Conversely, in a pilot study, enforced darkness (14 h, from 6 p.m to 8 p.m) for three consecutive days has been used as an adjunct treatment for mania. It was demonstrated that, when the duration of the current manic episode was shorter than two weeks, dark therapy was correlated with a rapid reduction of Young Mania Rating Scale scores (Barbini et al., 2005). These results suggest an interesting relationship between light and mood that may be mediated through the production and synthesis of melatonin. Melatonin in animals and humans acts as a chronobiotic cue for day-length related seasonal functions (Arendt and Skene, 2005). Patients with BD show reductions of melatonin in manic, depressed and euthymic states (Kennedy et al., 1996). Patients with TLE also have low melatonin which increases within 24 h following a PS (Bazil et al., 2000) and research involving animals has found that melatonin has anticonvulsant properties (Mevissen and Ebert, 1998).

Both PS and mania are influenced by hormonal variations. However, menstruation is a precipitating factor for PS but not for mania. This is surprising given that mood changes in the premenstrual phase are common even in healthy women. This is an area that warrants future research given that the rate of rapid cycling BD is higher in women than in men suggesting some relationship to hormonal fluctuations. Catamenial epilepsy is believed to relate to hormonal changes associated with the menstrual cycle. Specifically, estrogen is proconvulsant whereas progesterone is anticonvulsant (Reddy, 2009). The postpartum period is not a shared precipitating factor in these disorders. The postpartum period is marked by abrupt hormonal, psychological and social changes and is implicated in the onset and recurrence of mania in both women and men. This suggests environmental changes contribute to the development of postpartum mania.

Antidepressant medication are a precipitating factor for mania and PS. As mentioned previously, antidepressants may cause a lowering of the seizure threshold but the mechanism by which they may cause mood lability or mania are not well understood. This may be related to shared neurochemical underpinnings in the two disorders. Implicated in the pathogenesis of BD are dopamine, serotonin and possibly glutamate each of which are also believed to modulated epileptic activity (Amann and Grunze, 2005).

There are several limitations to the conclusions of this review. First, information on precipitating factors is derived from a variety of sources that typically examine individual factors from published epidemiological or clinical data. These may be identified using retrospective study methodology which includes asking participants to identify factors from a list, self-report, or by prospective studies involving longitudinal design. Given that the majority of evidence cited in this review is derived from retrospective accounts it is important to consider the associated limitations. These include the high potential for systematic bias of memories coupled with the process of effort after meaning. This is where patients place high valence on events that precipitated an episode in order to account for symptom exacerbations. In addition, patients may be asked to recall precipitating factors for past episodes further impacting upon the reliability of memories. In order to overcome these limitations prospective studies are particularly valuable although they are subject to high rates of attrition particularly when studying individuals with mania.

Of the 30 papers included in the review that provided information on precipitating factors in epilepsy, 10 specified and presented data on TLE patients as an identified subgroup. The remainder of papers either did not assess location of seizure adequately or did not analyze by subgroup. All these papers included information on the three precipitating factors identified as overlapping. The conclusions regarding the three overlapping precipitating factors

Table 1
Summary of main findings—precipitating factors.

Precipitating factor	Bipolar disorder	Epilepsy
Stress*	✓ Strong evidence by retrospective and prospective accounts relates stress to mania, possibly by the endocrinological response	✓ Strong evidence retrospective and prospective accounts relates stress to seizures. Most affected is PS from temporal lobes
Goal-attainment events	✓ Vulnerability for mania—higher life ambitions. Higher levels of manic symptoms after goal-attainment events	No evidence
Emotion**	✓ Tentatively associated more evidence needed as may confuse state and trait markers. Joy and amusement = greater manic symptoms. Lability in those whose relatives express high levels of expressed emotion	✓ In epilepsy excitement, fear, anger and anxiety—greater number of seizures. Strongly associated with PS in TLE
Sleep reduction*	✓ Sleep reduction serves as a marker for mania and depression. Animals and humans associated with manic-like behaviour and mania in BD. Prospective evidence to support sleep deprivation and switch to mania	✓ Associated with PS in TLE self-report. Seizure diaries—as little as 1.5 h in sleep reduction can result in greater number of seizures
Lunar phase	Associated with higher incidence of hospital admissions. No direct evidence in BD	No effect on epileptic seizures, possible effect on non-epileptic seizures
Seasonal variation	✓ Spring and summer are associated with mania in BD possibly due to the effect of light and/or sleep reduction	✓ Epileptiform discharges more common in winter. Seizures are more frequent in winter PS less common on bright sunny days
Puberty/ menarche	Related to the onset. No specific evidence as a precipitating factor	Possible predisposing factor inconsistent findings relating to menarche
Menstruation	Symptom fluctuations but not mania specifically, strong candidate for future research	✓ PS in TLE—catamenial epilepsy
Postpartum	✓ Associated with mania and psychosis	Possible predisposing factor
Peri/ menopause	Symptoms worsening/ fluctuations more research needed with hormonal level verifications. Possible predisposing factor	More research needed possible predisposing factor
Antidepressant medications*	✓ Mechanism unknown, suggestive of the role of neurotransmitters in the onset of mania	✓ Lowers the seizure threshold

* Denotes a shared precipitating factor in the two disorders.
** Tentative precipitating factor ✓ denotes a precipitating factor.

need to be considered in the light of the limited literature based on well-defined samples of TLE, which in this review comprised 10 papers. Assessing the data in these papers alone the case for the overlapping precipitating factors was not materially diminished. However findings in this area will be strengthened by careful attention to sample definition in future research.

Whilst beyond the scope of this review it is noteworthy that many of the secondary manias that occur in neurologic disorders (e.g., multiple sclerosis, traumatic brain injury, acquired immune deficiency syndrome) are also associated with seizures. This further strengthens the notion that the two disorders share underlying neural networks that result in episodes.

In summary, there is significant overlap between precipitating factors in mania and partial seizures. This is indicative of some common underlying pathways, which mediate the occurrence of episodes in these illnesses. The pathways highlighted by the review include those serving sleep, stress responses, antidepressant action and the effects of season. An understanding of precipitating factors is beneficial for patients and practitioners in formulating individual treatment plans and self-management of the conditions. In addition, health locus of control may be improved if a sense of greater predictability of episodes is perceived. Further research on precipitating factors common to both disorders may lead to refinement of clinical interventions targeting these, drawing on relevant findings from BD and epilepsy research to mutual benefit (Table 1).

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Conflict of interest

None of the authors have any current conflicts of interest to declare including any financial, personal or other relationships with people within three years of beginning the submitted work which would unduly influence the work.

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Chapter 3

Systematic review of cognitive function in euthymic bipolar disorder and pre-surgical temporal lobe epilepsy

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REVIEW
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Systematic Review of Cognitive Function in Euthymic Bipolar Disorder and Pre-Surgical Temporal Lobe Epilepsy

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Background: Bipolar disorder (BD) and temporal lobe epilepsy (TLE) overlap in domains including epidemiology, treatment response, shared neurotransmitter involvement and temporal lobe pathology. Comparison of cognitive function in both disorders may indicate temporal lobe mediated processes relevant to BD. This systematic review examines neuropsychological test profiles in euthymic bipolar disorder type I (BD-I) and pre-surgical TLE and compares experimental designs used.

Methods: A search of PubMed, PsychINFO, and Scopus using Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines was conducted. Inclusion criteria were comparison group or pre- to post-surgical patients; reported neuropsychological tests; participants aged 18–60 years. Fifty six studies met criteria: 27 BD-I; 29 TLE.

Results: Deficits in BD-I compared to healthy controls (HC) were in executive function, attention span and verbal memory. Deficits in TLE compared to HC were in executive function and memory. In the pre- to post-surgical comparisons, verbal memory in left temporal lobe (LTL) and, less consistently, visuospatial memory in right temporal lobe (RTL) epilepsy declined following surgery. BD-I studies used comprehensive test batteries in well-defined euthymic patients compared to matched HC groups. TLE studies used convenience samples pre- to post-surgery, comparing LTL and RTL subgroups, few included comparisons to HC (5 studies). TLE studies typically examined a narrow range of known temporal lobe-mediated neuropsychological functions, particularly verbal and visuospatial memory.

Conclusion: Both disorders exhibit deficits in executive function and verbal memory suggestive of both frontal and temporal lobe involvement. However, deficits in TLE are measured pre- to post-surgery and not controlled at baseline pre-surgery. Further research involving a head-to-head comparison of the two disorders on a broad range of neuropsychological tests is needed to clarify the nature and extent of cognitive deficits and potential overlaps.

Keywords: bipolar disorder, temporal lobe, focal seizures neuropsychology, cognition, epilepsy, systematic review

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INTRODUCTION

Bipolar disorder type I (BD-I) is typically characterized by episodes of mania and depression with inter-episode euthymia. A number of impairments have been noted in the euthymic phase of the illness including social, occupational functioning, and cognitive deficits (1, 2).

Most studies have examined cognitive deficits in euthymic patients with BD-I compared to healthy controls (HC). Five meta-analyses have reported impairments in cognitive domains of executive functioning (3–7), verbal memory (3, 5–7), visuospatial memory (7), and attention (4, 6). One meta-analysis found no impairment of verbal memory and executive function in BD-I compared to HC (8). An individual patient data meta-analysis by Bourne et al. (9) reported impaired verbal memory and attention in euthymic BD-I patients relative to HC (9). The absence of an association between cognitive impairment and medication dose in euthymic BD-I patients suggest the effects of medication do not fully account for the cognitive impairments observed (4). These meta-analyses support the assumption that cognitive impairments exhibited in the euthymic phase are trait markers of the disorder.

An alternate research design is to compare and contrast cognitive deficits in BD-I to a reference condition which shares common features. For example, a meta-analysis comparing BD-I and schizophrenia reported more pronounced cognitive deficits in schizophrenia on measures of verbal fluency, verbal memory, executive function, visuospatial memory, mental speed, IQ, and concept formation (10). Similarly a single study comparing BD-I, obsessive compulsive disorder reported impaired verbal and episodic memory compared to HC (11). The BD-I group had greater impairments in learning word lists and delayed recall. These results suggest the importance of the temporal lobes in both disorders in the consolidation and retrieval of memories.

A single study compared BD-I with complex partial seizure disorder (12). It is noted that the classification of epilepsy syndromes has been subject to a number of iterations. In this review, we use the most commonly reported and widely understood term "temporal lobe epilepsy (TLE)" to incorporate the terms complex partial seizure disorder and focal seizures arising from the temporal lobes. The Jones et al. study reported greater impairment of executive function, attention and delayed verbal recall in the TLE group. These results should be interpreted with caution given the small and unequal sample sizes (BD-I $n = 26$, TLE $n = 9$). A case can be made for further exploration of similarities and differences between the neuropsychological test profiles seen in euthymic BD-I and interictal TLE. This is particularly so given the localizing pathology of TLE, which allows inferences to be made regarding the contribution of temporal lobe processes to the range of cognitive deficits reported in BD-I.

There are a number of established similarities between BD-I and TLE. These typically include a chronic course punctuated by episodic manifestations of mania and seizures, respectively. Other similarities include: the proposed involvement of kindling mechanisms (13); changes in neurotransmitters (excitatory amino acids, GABA, dopamine and serotonin), voltage-opened ion channels (sodium, calcium and potassium) and second messenger systems (G-proteins, phosphatidylinositol, protein kinase C, myristoylated alanine-rich C kinase substrate), and treatment response to antiepileptic medications in both disorders (14).

In addition, episodes in both disorders commonly feature sensory, perceptual, cognitive, and affective changes (15) including depression (16). Epidemiological studies have shown that the proportion of BD-I among people with epilepsy is more than twice as high as in the general population (17) and that mania is more common in patients with TLE than in the general population (18). BD-I is also associated with comorbid epilepsy but not parental epilepsy (19). Episodes of mania in BD-I and seizures in TLE share precipitating factors including stress, sleep reduction and antidepressant medications (20).

The temporal lobes have also been the subject of neuroimaging research in both disorders. In BD-I many studies have investigated correlates of the disorder to specific brain regions. Meta-analyses of magnetic resonance imaging (MRI) studies have reported that BD-I is associated with right lateral ventricular enlargement (21) and an enlarged left amygdala (22). However, studies of temporal lobe size are inconsistent; with reported increases (23), reductions (24) or no differences (25–28) likely reflecting the difficulties of defining and measuring the volume of individual cerebral lobes on MRI.

In TLE, MRI studies have reported structural brain abnormalities in the hippocampus, entorhinal cortex (29), thalamus (30), and fornix (31). On voxel-based morphometry, TLE is associated with gray matter pathology in the hippocampus, cingulum, thalamus, and frontal lobes. White matter reductions ipsilateral to the seizure focus were also found in the temporopolar, entorhinal, and perirhinal areas (32). Typically, TLE originates unilaterally from the medial temporal lobe; they may, however, be propagated from other regions which project to limbic areas (33).

Given these potential diffuse structural abnormalities seen in patients with TLE, it could be expected that neuropsychological deficits may not be limited to tasks involving temporal lobe function. Patients with TLE display deficits in memory, general intelligence, language, executive function, and motor speed relative to HC (34, 35). Deficits in verbal memory, language, and psychomotor speed may be affected by factors such as age of onset of epilepsy, general intelligence, the number and dose of antiepileptic medications used, and seizure frequency (35).

The literature describing clinical features, imaging findings, and neuropsychological test profiles is largely in a separate corpus for BD-I and for TLE with only one small study directly comparing the two (12).

The current structured review brings these two bodies of work together in a comparison of the neurocognition literature findings of the two conditions side-by-side. The aim is to determine whether and to what extent the cognitive impairments seen in euthymic BD-I are mirrored by those attributed to a pathology primarily affecting the temporal lobes, that is TLE.

METHOD

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (36).

Inclusion criteria: (a) controlled comparison, (b) patients diagnosed with BD-I as assessed by a recognized criterion-based diagnostic system, (c) BD-I patients rated as euthymic, defined by their scores on a rating scale (<8 HamD, <8 YMRS); patients with unilateral TLE, from any cause, with diagnosis confirmed in a pre-surgical workup, (d) at least one neuropsychological test, (e) adult participants (18–60 years), (f) in the case of more than one article by the same authors results were not identified as being from the same sample, (f) articles published 1980 or later.

Identification of Studies

A comprehensive search of the electronic databases PubMed, PsychINFO, and Scopus for peer-reviewed articles published in English was conducted in the last week of May 2016. Search terms were grouped as follows: bipolar, manic depress*, baseline, asympt*, remit*, stable (group 1); or epilep*, seizure, presurg*, temporal, focal, partial, complex, interictal (group 2) and WAIS, Wechsler, trail making, continuous performance, stroop, digit span, verbal learning, rey, working memory, benton, card sort*, verbal fluency, RAVLT, CAVLT, tower of London (group 3). These search terms were combined as follows: group 1 AND group 3 for BD-I and group 2 AND group 3 for TLE.

Data Extraction

The abstracts located from the search strategy were entered into EndNoteX7. The PRISMA flowchart (**Figure 1**) sets out the steps in screening conducted by author EB. After the screening of titles and abstracts the remaining 139 studies were examined in full text, using a purpose built coding sheet to assess whether they met inclusion criteria. This process resulted in the study sample of 56, of which 27 related to BD-I and 29 to TLE.

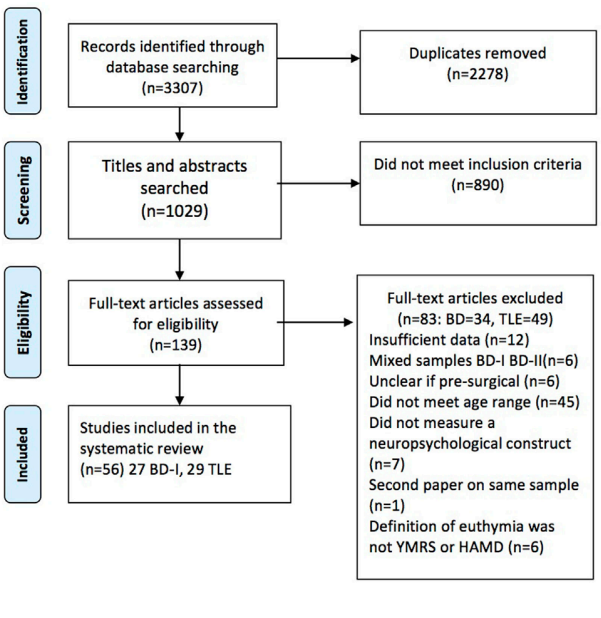

FIGURE 1 | Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram of included studies.

RESULTS

The search strategy identified an initial 3,307 articles of which 56 met inclusion criteria, 27 related to BD-I and 29 to pre-surgical TLE. Studies of BD-I are summarized in **Table 1** and of TLE in **Table 2** detailing authors, sample sizes, medication (BD-I only as this was not recorded in the TLE samples), neuropsychological test parameters, and summary results.

As demonstrated in **Table 1**, 25 of 27 studies compared patients with BD-I ($n = 1{,}398$) to HC ($n = 1{,}142$). The remaining studies compared manic, euthymic, and depressed groups. The most commonly reported impairments in BD-I were in executive function, attention span, and verbal memory. No studies found enhanced neuropsychological function in euthymic BD-I.

As shown in **Table 2**, in the epilepsy literature, all of the TLE studies compared neuropsychological test performance pre- to post-surgery. Only 5 of the 29 studies compared pre-surgical TLE ($n = 150$) to HC ($n = 111$); these studies found significant impairments in TLE compared to HC on tests of memory and executive function.

In 26 of the TLE studies, the samples were divided by laterality of seizure focus with the primary pathology affecting the right temporal lobe (RTL $n = 846$) or the left temporal lobe (LTL $n = 1{,}068$). In pre-surgical TLE, the direct comparison of LTL and RTL groups indicated that the LTL group showed impaired verbal memory and the RTL group, less consistently, impaired visuospatial memory.

The most common impairment observed in TLE related to surgery was in verbal memory. This finding was also associated with laterality, 24 studies reporting decline in verbal memory from pre- to post-surgery in LTL patients, whereas in RTL there was a less consistent decline in visuospatial memory. No significant differences in attention were found for laterality or pre- to post-surgery in TLE.

Table 3 shows the results of individual neuropsychological tests that were reported in more than one study, for BD-I and TLE. Of note, the total number of neuropsychological tests used across all studies differed between BD-I (27) and TLE (11); this was not evenly distributed across cognitive domains. The number of studies where any executive function instrument was administered in TLE was only 4 (2 WCST, 2 COWAT) of 29 compared to 21 of 27 in BD-I. One study compared RTL, LTL and HC and showed that all patients were impaired on the WCST relative to HC (87). The number of studies where any verbal memory instrument was administered was 26 of 29 in TLE compared to 14 of 27 in BD-I. The comparable figures for visuospatial memory instruments were 25 of 29 in TLE and 11 of 27 in BD-I. Similarly, only 6 studies measured attention in TLE compared to 17 studies in BD-I. Thus, while both fields have seen sustained research activity in identifying neuropsychological deficits, the focus of inquiry in TLE has been on verbal and visuospatial memory and in BD-I executive function.

Notwithstanding the differences in the intensity and focus of neuropsychological testing in both conditions, consistent results emerging from this study emphasize deficits in verbal memory, which have been reported in the majority of studies that have examined this area in both BD-I and TLE.

TABLE 1 | Summary of included studies on euthymic bipolar disorder.

Reference	*n*	Medications bipolar sample	Neuropsychological test parameters	Results
Altshuler et al. (37)	BD 40 SZ 20 HC 22	Li 25, AC 12, AD 4, AP 6, BZD 3	WAIS-R block design, vocab; TMT, WCST, Stroop; VFT, CVLT; ROCFT; Star mirror tracing Task, PR	BD impaired verbal memory and executive functioning
Bas et al. (38)	BD 60 HC 41	Li 39, AP 37, LTG 9, VPA 21	Stroop, TMT A and B; WMS-R visual reproduction; RAVLT	BD impaired on RAVLT
Bora et al. (39)	BD 514 BD-II 42 HC 416	Li 63.2%, VPA 47.6%, AP 47.2%, AD 5.7%	Stroop. WCST	Deficits exist in subgroups who have severe and global cognitive deficits
Chang et al. (40)	BD 23 BD-II 23 HC 23	BD Li 13, AP 15, LTG 7, VPA 9	WAIS-R block design and vocab; CVLT, VFT	All NS
Chou et al. (41)	BD 23 HC 33	AP 13, VPA 19	The Color Trails Test, WCST; WMS-III – Word Lists Test, Face Test; Go/No-GO, Test for Attentional Performance	BD impaired faces memory and WCST
Deckersbach et al. (42)	BD 25 HC 25	Li 11, AC 9, AD 9, AP 3	ROCFT	Immediate recall BD impaired, copy and recognition preserved
Deckersbach et al. (11)	BD 30 Obsessive compulsive disorder 30 HC 30	Li 13, AC 11, AD 8, AP 4	CVLT	CVLT BD impaired learning and delayed free recall
Dell'Osso et al. (43)	BD 15 BD-II13 HC 27	BD Mono 2, Poly 12	N-Back	NS HC and BD
Dittmann et al. (44)	BD 65 BD-II 38 HC 62	BD Li 27, AD 10, AP 33, CBZ 4, VPA 28	TMT; HAWIE-R; WAIS-III letter number sequencing; RBANS	Psychomotor speed, working and delayed memory, verbal learning, executive functioning BD impaired
Dixon et al. (45)	BD manic 15 dep 15, eu 15, HC 30	Eu Li 15, AD 8, AP 10, AC 2	WAIS-R Vocab; Stroop; FAS; Hayling sentence completion test; Cognitive Estimates Test	VF total responses, Hayling response initiation latency, error score and using strategy, stroop EuBD impaired
Doganavşargil-Baysal et al. (46)	BD 60 HC 20	Li 11, MS + AP 12, 2MS 12, VPA 6	WCST, TMT, Stroop; RAVLT; Cancelation test	Significant differences on all measures between BD and HC
Doganavşargil-Baysal et al. (46)	BD 54 HC 18	Li 10, MS + AP 27, 2MS 11, VPA 5	WCST; RAVLT	Both measures BD < HC
Doruk et al. (47)	Manic 20 Dep10 Eu 21	Unknown	Stroop; Serial Digit Learning Test; RAVLT; Cancelation Test	NS HC and EuBD
Fistikci et al. (48)	BD 25 HC 25	Li 25	WCST; Montreal Cognitive Assessment	NS HC and BD
Frangou et al. (49)	BD 10 Un offspring 15 HC 43	Li 5, AC 3	WCST; Hayling sentence completion	WCST BD and offspring made more errors
Hsiao et al. (50)	BD 30 BD-II 37 HC 22	VPA 29	WAIS-III digit symbol; TMT; WMS-III	Verbal memory, working memory, psychomotor speed, executive function BD impaired
Martino et al. (51)	BD 48 BD-II 37 HC 34	AD 16, AP 28, BZD 23, MS 48	WAIS vocab, digit span; TMT, WCST, IGT; Memory battery of Signoret	Verbal memory, attention and executive functions impaired
Muralidharan et al. (52)	BD 72 HC 40	AP 27, Li 34, VPA 38	TMT, Stroop; CANTAB; CVLT; WMS-III LNS	P on VPA more working memory deficits than Li or HC
Muralidharan et al. (53)	BD 68 HC 38	AP 51, Li 32, MS + AP 50, VPA 32	TMT, Stroop; CANTAB; CVLT; WMS-III letter number sequencing	Verbal and visuospatial memory, working memory and executive function BD impaired.
Normala et al. (54)	BD 40 HC 40	AP 6, MS 11, MS + AD 1, MS + AP22	WAIS Digit span; TMT; Verbal Fluency	Executive and attention functioning BD impaired

(*Continued*)

TABLE 1 | Continued

Reference	*n*	Medications bipolar sample	Neuropsychological test parameters	Results
Pattanayak et al. (55)	BD 30 HC 20	AP 5, LTG 2, Li 21, VPA 11	VIQ; TMT, Stroop; N-Back; Postgraduate Institute Memory Scale	Attention, information processing speed, executive function, verbal memory BD impaired
Radwan (56)	BD 30 HC 30	Unknown	WAIS; WCST; WMS; CPT	All BD impaired
Sepede et al. (57)	BD 24 Unaffected rels 33 HC 24	AD 10, AP 15, BZD 8, Li 3, MS 9	CPT	Sustained attention impaired BD and rels
Trivedi et al. (58)	BD 15 HC 15	CBZ 1, Li 8, VPA 6	WCST; SWMT; CPT	Executive function BD impaired
Trivedi et al. (59)	BD 15 SZ 15, HC 15	Unknown	WCST; SWMT; CPT	Executive function BD impaired
Yates et al. (60)	BD dep 34 BDEu 31, HC 34	AD 9, AP 18, BZD 9, MS 29	WAIS-III	Verbal measure BD impaired
Zubieta et al. (61)	BD 15 HC 15	AP 3, CBZ 2, Li 7, VPA 12	WAIS-R: digit span; WCST, Stroop; WMS-R; verbal fluency; test of variable attention	Verbal learning, executive function, motor coordination and sequential memory BD impaired. NS verbal fluency or attention

BD, bipolar; BD-II, bipolar II; HC, healthy controls; SZ, Schizophrenia; Li, lithium; AC, anticonvulsant; AD, antidepressant; AP, antipsychotics; BZD, benzodiazepine; CBZ, carbamazepine; LTG, lamotrigine; MS, mood stabilizer; VPA, valproate; Mono, monotherapy; Poly, polytherapy; AMIPB, Adult Memory and Information Processing Battery; BVRT, Benton Visual Retention Test; VLMT, Verbaler Lern- und Merkfähigkeitstest; DCS-R, Diagnosticum für Cerebralschädigung – II; NAART, North American Adult Reading Test; WRAT, Wide Range Achievement Test; WAIS, Wechsler Adult Intelligence Scale; CPT, Continuous Performance Test; CVLT, California Verbal Learning Test; RAVLT, Rey Auditory Verbal Learning Test; WCST, Wisconsin Card Sorting Test.

DISCUSSION

To our knowledge, this is the first systematic review directly comparing the literature on cognitive function in BD-I and TLE. Consistent with the meta-analyses of cognition in euthymic BD-I, our review showed impairments on a wide range of cognitive measures. In the individual studies reviewed, the most commonly reported impairments in BD-I were in executive function, attention span, and verbal memory. The impairments of executive function in patients with BD-I may be suggestive of an underlying dysfunction in the prefrontal cortex (3).

In TLE studies, a decline in pre- to post-surgery in verbal memory was commonly reported in patients with seizures originating from the LTL, and less consistently, in visuospatial memory in patients with RTL epilepsy. Functional MRI studies have revealed that the right hemisphere is associated with spatial memory (91). In our sample, executive function was not widely examined in patients with epilepsy; however, an impairment was found. For executive function, two instruments were employed across four studies, three of which showed a difference between pre- to post-surgery scores and one study found impaired performance in TLE relative to HC participants.

In keeping with our results, meta-analyses of memory function pre- to post-surgery reported that, following a resection of the LTL, a clear decline in verbal memory is observed, an effect that is particularly salient for immediate verbal recall. However, the pattern of impairment following partial resection of the RTL showed a trend for improvement on tasks of non-verbal memory (92). This suggests that memory impairments are state markers affected by seizures and abnormalities in the temporal lobes. Other factors that affect cognitive performance in TLE are the chronicity of the condition, older age, lower intellect, and greater abnormalities shown on imaging (92). Another meta-analysis found that the evidence regarding post-surgery outcome on visuospatial memory following right anterior temporal lobectomy was less clear (93).

In TLE, it is unclear whether frontal lobe impairments shown on executive function measures are a product of temporal lobe involvement or are a side effect of the propagation of epileptic activity from the epileptic zone (94). Other evidence has suggested that the prefrontal cortex, in particular the orbitofrontal cortex, is influenced by ictal discharges from the mesial temporal lobe (95). Some studies have shown that the temporal neocortex is implicated in executive function implying that a frontotemporal network is used for processing information (96).

This review emphasizes that prior research on cognitive impairments in the fields of BD-I and TLE has employed methodologies that reflect different research questions. The BD-I literature predominantly examines cognition as a characteristic of the disorder itself, on a par with symptoms and potentially amenable to therapeutic intervention. The TLE literature is concerned with the effects of ablative surgery that aims to remove seizure foci but may consequently also directly affect healthy brain tracts. It addresses whether cognitive function improves or declines subsequent to surgery and the moderating effects of laterality.

The majority of BD-I studies compare euthymic patients with HC, whereas in the epilepsy studies, patients act as their own controls in relation to surgical intervention and laterality. In addition, given that the BD-I studies are interested in trait markers in the euthymic phase, they routinely report the quantitative differences between patients and HC, rendering the results suitable for incorporation in meta-analytic studies. The TLE literature has focused

TABLE 2 | Summary of included studies on pre-surgical temporal lobe epilepsy (TLE).

Reference	*n*	Neuropsychological test parameters	Results
Baxendale and Thompson (62)	Right temporal lobe (RTL) 133 LTL 157	WAIS PIQ, VIQ; AMIPB	Verbal memory decline post-surg left temporal lobe (LTL)
Baxendale et al. (63)	RTL 146 LTL 177	WAIS PIQ, VIQ; AMIPB; Birt Memory and Information Processing Battery	RTL and LTL at equal risk of post-surg decline
Berenbaum et al. (64)	LTL 57	WAIS Digit Span; CVLT	CVLT decline post-surg
Bjørnaes et al. (65)	RTL 50 LTL 41	WAIS Digit Span; Benton Visual Retention Test (BVRT); Design Learning and Retention Test; Verbal List Learning and Retention; Tactual Performance Test	Improvement at 2-year follow up post-surg
Chelune et al. (66)	RTL 19 LTL 23	WAIS-R VIQ, PIQ; WMS-R, RAVLT; COWAT, Halstead-Wepman Aphasia Screening Exam, BNT, Speech Sounds Perception Test; Hooper Visual Organization Test, Seashore Rhythm Test	LTL decline post-surg
Chiaravalloti et al. (67)	RTL 16 LTL 10	WMS-III Faces Subtest; Graduate Hospital Facial Memory Test	RTL < LTL both pre- and post-surg
Chiaravalloti (68)	RTL 42 LTL 28	CVLT; Graduate Hospital Facial Memory Test	Verbal memory post-surg decline LTL, RTL improved. Visuospatial memory post-surg decline RTL, LTL improvement
Fernandes et al. (69)	RTL 23 LTL 24 healthy controls (HC) 28	WAIS-R Block design, Vocabulary; WMS-R; RAVLT	Cognitive scores post-surg decline low pre-surg scores. Non-verbal memory post-surg RTL decline, verbal and visuospatial memory LTL decline
Giovagnoli et al. (70)	RTL 12 LTL 12 HC 36	Raven's Colored Progressive Matrices; Attentive Matrices; Verbal Selective Reminding Procedure, Story Recall, Verbal Memory Distractor Test; Visual Selective Reminding Procedure, ROCFT, Visual Memory Distractor Test	Verbal memory pre- and post-surgery LTL impaired relative to HC. Visual deficits present in both groups relative to HC
Gleissner et al. (71)	RTL 63 LTL 52	VLMT; DCR-S	Verbal memory LTL decline
Glosser et al. (72)	RTL 13 LTL 8 HC 10	Boston Naming Test; CVLT Benton Facial Recognition, Graduate Hospital Facial Memory	Recognition of familiar faces and learning new faces RTL impaired. Names of familiar faces LTL impaired
Helmstaedter et al. (73)	LTL 47	Verbal Learning and Memory Test; RAVLT	Delayed recall and recognition post-surg improvement
Hermann and Wyler (74)	RTL 14 LTL 15	COWAT; Token Test	Language tests pre-surg LTL deficit
Hermann et al. (75)	RTL 31 LTL 26	CVLT	Verbal memory post-surg RTL increased
Hermann et al. (76)	RTL 26 LTL 36	WAIS-R Digit Span; Multilingual Aphasia Examination Visual Naming Test; CVLT	CVLT post-surg decline LTL
Köylü et al. (77)	RTL 12 LTL 14	List learning task	LTL post-surg decline
Lee et al. (78)	LTL 38	RAVLT; ROCFT	Memory post-surg decline
Loring et al. (79)	RTL 13 LTL 16	Selective Reminding Test, Serial Digit Learning, ROCFT, Form Sequence Learning	Complex figure RTL impaired. Verbal memory decline LTL
Malikova et al. (80)	RTL 11 LTL 26	WAIS-R; WMS-R; Verbal Fluency Test	FSIQ, global and verbal memory, attention, and working memory all improved post-surg
Morino et al. (81)	RTL 31 LTL 31	WMS-R; Miyake Verbal Retention Test; BVRT	Memory RTL improved post-surg. Verbal memory LTL post-surg improved
Quigg et al. (82)	RTL 16 LTL 14	TMT; BNT; CVLT; WMS-R Logical Memory Scale	BNT and CVLT LTL decreased post-surgery. Language and verbal memory LTL increased. TMT increased
Seidenberg et al. (83)	RTL 30 LTL 46	CVLT	Free recall LTL decline post-surgery

(*Continued*)

TABLE 2 | Continued

Reference	*n*	Neuropsychological test parameters	Results
Selwa et al. (84)	RTL 14 LTL 17 Non-surgical TLE 28	WAIS-R; WMS	FSIQ, Logical Memory RTL improved post-surg. Verbal memory decline LTL post-surg
Shamim et al. (85)	RTL 14 LTL 16	WAIS-III; WMS-III	Verbal memory deficit post-surg LTL
Stretton et al. (86)	RTL 17 LTL 16 HC 15	WAIS-III Digit Span; Gesture Span Task; Motor Sequences Task; Dot-Back Paradigm	Working memory pre-surg RTL and LTL worse than HC. WM improved post-surg LTL
Tisser et al. (87)	RTL 10 LTL 15 HC 22	WAIS-R; WCST	WCST RTL and LTL impaired, improved post-surg
Trenerry and Jack (88)	RTL 34 LTL 34	WAIS-R; WCST	The WCST is not useful for lateralizing seizure onset in TLE
Trenerry et al. (89)	RTL 36 LTL 44	WAIS-R; WMS-R; RAVLT; Visual Spatial Learning Test	Verbal and visual memory LTL improved post-surg
von Rhein et al. (90)	RTL 20 LTL 32	VLMT; DCS-R; BNT; Token Test	Verbal Memory impaired post-surgery. Naming decline post-surgery LTL

Tests of executive function: WCST, FAS, TMT-B, Stroop, Hayling Sentence Completion Test, CANTAB: Intra Extra Dimensional Set Shifting, CANTAB: Stockings Problem; Tests of Verbal Memory—CVLT, RAVLT, WAIS Vocab, WMS-R: Logical Memory, WMS-R: Verbal Paired Associates, Token Test, VLMT: Verbaler Lern- und Merkfähigkeitstest; Tests of non-verbal memory- ROCFT, WMS: Visual reproduction, WMS-R: Design Memory, WMS-R Visual Reproduction, WMS-III: Face Test, CANTAB: Spatial recognition memory, CANTAB: Pattern Recognition Memory, CANTAB: Paired Associates Learning; Attention span WAIS: Digit Span, Adult Memory and Information Processing Battery (AMIPB); sustained attention CPT; working memory SWMT, N-Back, WAIS: Letter Number Sequencing, WMS-III: Letter Number Sequencing, CANTAB: Spatial Working Memory.

TABLE 3 | Neuropsychological test findings summary table (for tests used more than once) in studies of bipolar disorder (BD) and temporal lobe epilepsy (TLE).

Measure	BD		TLE		Pre- to post-surgical		Laterality effects
	Use in studies, number of participants BD	BD < HC sig	Use in studies, number of participants TLE	sig	↑	↓	
Executive function							
WCST	12 studies BD *n* = 859, healthy controls (HC) *n* = 676	11	2 studies Right temporal lobe (RTL) *n* = 44, left temporal lobe (LTL) *n* = 49, HC *n* = 22	1	↑1		
COWAT(FAS)	5 studies BD *n* = 133, HC *n* = 130	2	2 studies RTL *n* = 33, LTL *n* = 38	2	↑1		Higher score LTL group pre- assoc. with greater impairment post-surg
TMT-B	9 studies BD *n* = 513, HC = 339	7					
Stroop	10 studies BD *n* = 895, HC = 642	7					
Hayling Sentence Completion Test	2 studies BD *n* = 25, HC *n* = 73	2					
CANTAB: Intra Extra Dimensional Set Shifting	2 studies BD *n* = 140, HC *n* = 78	2					
CANTAB: Stockings Problem	2 studies BD *n* = 140, HC *n* = 78	2					
Verbal memory							
CVLT	5 studies BD *n* = 233, HC *n* = 153	3	7 studies RTL *n* = 158, LTL *n* = 215, HC *n* = 10	6		↓6	Post-surg LTL decline 6 RTL > LTL 1

(*Continued*)

TABLE 3 | Continued

Measure	BD		TLE		Pre- to post-surgical		Laterality effects
	Use in studies, number of participants BD	BD < HC sig	Use in studies, number of participants TLE	sig	↑	↓	
RAVLT	3 studies BD *n* = 141, HC = 79	2	5 studies RTL *n* = 78, LTL *n* = 176, HC *n* = 28	5		↓5	Post-surg LTL decline 5
Verbal comprehension: WAIS Vocab	4 studies BD *n* = 187, HC *n* = 173	0					
WMS-R: Logical Memory			6 studies RTL *n* = 206, LTL *n* = 256, HC *n* = 28	4	↑3	↓1	LTL < RTL 1
WMS-R: Verbal Paired Associates			4 studies RTL *n* = 119, LTL *n* = 151, HC *n* = 28	4	↑2	↓1	LTL < RTL 1
Token Test			2 studies RTL *n* = 34, LTL *n* = 47	1	↑1		Post-surg LTL improved 1
VLMT: Verbaler Lern- und Merkfähigkeitstest			2 studies RTL *n* = 83, LTL *n* = 82	2		↓2	
Visuospatial memory							
ROCFT	2 studies BD *n* = 65, HC *n* = 47	0	3 studies RTL *n* = 25, LTL *n* = 62, HC *n* = 36	2	↑1		LTL < RTL 1
WMS: Visual reproduction	3 studies BD *n* = 105, HC *n* = 78	0	2 studies RTL *n* = 27, LTL *n* = 29	0			
CANTAB: Spatial recognition memory	2 studies BD *n* = 140, HC *n* = 78	2					
CANTAB: Pattern Recognition Memory	2 studies BD *n* = 140, HC *n* = 78	2					
CANTAB: Paired Associates Learning	2 studies BD *n* = 140, HC *n* = 78	2					
WMS-R: Design Memory			4 studies RTL *n* = 78, LTL *n* = 93, HC *n* = 28	2	↑1	↓1	RTL decline 1
WMS-R Visual Reproduction			5 studies RTL *n* = 241, LTL *n* = 484, HC *n* = 28	2	↑1	↓1	RTL decline 1
WMS-III: Face Test			1 study RTL *n* = 16, LTL *n* = 10	1		↓1	RTL decline 1
Graduate Hospital Facial Memory			3 studies RTL *n* = 71, LTL *n* = 46, HC *n* = 10	3	↑1		RTL < LTL 2
Benton Visual Retention			2 studies RTL *n* = 31, LTL *n* = 72	0			
Diagnosticum für Cerebralschädigung			3 studies RTL *n* = 83, LTL *n* = 253	2		↓1	
Spatial ability							
WAIS: Block design	4 studies BD *n* = 124, HC *n* = 109	0					
Attention span							
WAIS: Digit Span	3 studies BD *n* = 103, HC *n* = 89	2	4 studies RTL *n* = 93, LTL *n* = 150, HC *n* = 15	0			
TMT-A (also processing speed)	10 studies BD *n* = 513, HC = 339	8					
WAIS: Digit Symbol (also processing speed)	3 studies BD *n* = 91, HC = 86	3					
CANTAB: Rapid Visual Information	2 studies BD *n* = 140, HC *n* = 78	2					

(*Continued*)

TABLE 3 | Continued

Measure	BD		TLE		Pre- to post-surgical		Laterality effects
	Use in studies, number of participants BD	BD < HC sig	Use in studies, number of participants TLE	sig	↑	↓	
Adult Memory and Information Processing Battery (AMIPB)			2 studies RTL *n* = 279, LTL *n* = 334	2	↑1	↓1	
Sustained attention							
CPT	4 studies BD *n* = 84, HC *n* = 84	2					
Working memory							
SWMT	2 studies BD *n* = 30, HC *n* = 30	0					
N-Back	2 studies BD *n* = 45, HC *n* = 47	0					
WAIS: Letter Number Sequencing	3 studies BD *n* = 126, HC *n* = 126	3					
WMS-III: Letter Number Sequencing	2 studies BD *n* = 140, HC *n* = 78	3					
CANTAB: Spatial Working Memory	2 studies BD *n* = 140, HC *n* = 78	2					

↑ refers to an increase, ↓ a decrease from pre- to post-surgery, sig refers to the number of studies with a significant result, laterality comments only significant main effects or interactions are discussed.

on statistically significant differences pre- to post-surgery and has not reported information in a form suitable for meta-analysis of pre-surgical cognitive functioning. Therefore, we have employed a systematic review methodology to examine and compare the profile of cognitive deficits in the two conditions. As indicated in the Section "Results," the focus of inquiry of the neuropsychological tests employed in the BD-I studies is predominantly on frontal lobe functions and in TLE on verbal and visuospatial memory.

There are significant differences in the experimental designs examining cognition in the two patient groups. In BD-I studies, cognition is tested broadly with a wide range of measures, with a HC comparison group and statistical control for medication use. This allows for observed deficits to be interpreted as trait markers of BD-I. This is further supported by familial studies that show similar patterns of impairments among family members and patients (89). By contrast, studies assessing cognitive performance in pre-surgical patients with epilepsy do so generally without HC. Only five studies included HC ($n = 111$), consequently the findings have limited depth compared to those in the BD-I literature ($n = 1{,}142$). The pre-surgical neuropsychological workup consists mostly of tests of memory function, which is not surprising given that the surgery involves removing parts of or the whole temporal lobe.

In general, the studies on BD-I report the types of medications taken by patients at the time of testing (as shown in **Table 1**), which may have impacted the results. By contrast, in the epilepsy samples, it was typically not reported whether patients were receiving medication at the time of testing. A study that examined the effects of atypical antipsychotics on cognition in euthymic BD-I patients found that untreated patients showed better performance than those taking medication (93). Many patients with BD-I are treated with anticonvulsants that may worsen or enhance cognition (97). Of the total sample of 884 patients with BD-I included in the systematic review, 299 were taking lithium at the time of testing. A review of the effects of lithium on cognition found that impairments on tasks of psychomotor speed and verbal memory were present, whereas no effect was found on visuospatial ability or attention (97). Thus, cognitive performance may be impaired in various ways by different medications. A recent randomized crossover study examined the effects of methylene blue on cognition and mood-related symptoms in euthymic BD-I and BD-II. Neither low (15 mg) control doses nor high active doses (195 mg) had a significant effect on cognition (98). In rats, methylene blue prevents methylmalonate-induced seizures and oxidative damage in the striatum (99) providing interesting leads for future research into the overlaps between BD and epilepsy.

While this paper has provided an overview of the literature, it is subject to a number of limitations. One such factor is the differences of experimental designs in BD-I and TLE, which meant that a head-to-head meta-analytic comparison was not feasible. As discussed previously, the effect of medication was not uniformly controlled in BD-I and was either not reported or not systematically recorded in the epilepsy samples. In order to determine whether cognitive deficits are related to the illness and not undesirable side effect of medication, examination of otherwise stable drug-free patients would be of interest. The period of time between episodes (mania, depression, or seizures), time of testing, hospitalizations, and the presence of psychotic features were not considered in this review. In BD-I patients, the presence of sub-clinical symptoms is common, even in those patients who are rated as euthymic at the time of testing and may have impacted performance overall (3).

Although there is wide variation in the diagnostic criteria of euthymia, our study aimed to control for this by using the HAMD and YMRS as cutoffs; however, longitudinal measurements would have been advantageous to characterize proximity to manic or depressive episodes. Residual mood symptoms are also an important consideration in epilepsy where depression is the most common psychiatric comorbidity (18). In community-based samples, the rates of depression in epilepsy range from 20 to 30% and in hospital samples 20–55% (100, 101). It has been established that depression can cause cognitive impairments, particularly in the domains of attention, psychomotor activity, and memory all of which were relevant to this review (102).

We suggest a strong case may be made for a study comparing neuropsychological tests to assess deficits in BD-I, TLE, and matched HC. In future research, a comprehensive test battery employing tests of attention, executive function, memory, and psychomotor speed, coupled with imaging techniques, should be employed in both disorders relative to HC. This would provide valuable information on the effects of both BD-I and TLE on temporal and other cerebral areas as well as the effects of medication on neuropsychological test parameters. This would also be of value in identifying putative temporal lobe involvement in BD-I.

AUTHOR CONTRIBUTIONS

EB, KK, MG, and BT contributed to the design of the project, the analysis and discussion of the results and write up of the paper with KK, MG, and BT contributing their specialist perspective. EB and KK assessed the suitability of papers for inclusion in the manuscript and contributed to the PRISMA review.

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Chapter 4

The Current Status of the Ketogenic Diet in Psychiatry

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REVIEW
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The Current Status of the Ketogenic Diet in Psychiatry

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Background: The ketogenic diet (KD) has been used in treatment-resistant epilepsy since the 1920s. It has been researched in a variety of neurological conditions in both animal models and human trials. The aim of this review is to clarify the potential role of KD in psychiatry.

Methods: Narrative review of electronic databases PubMED, PsychINFO, and Scopus.

Results: The search yielded 15 studies that related the use of KD in mental disorders including anxiety, depression, bipolar disorder, schizophrenia, autism spectrum disorder (ASD), and attention deficit hyperactivity disorder (ADHD). These studies comprised nine animal models, four case studies, and two open-label studies in humans. In anxiety, exogenous ketone supplementation reduced anxiety-related behaviors in a rat model. In depression, KD significantly reduced depression-like behaviors in rat and mice models in two controlled studies. In bipolar disorder, one case study reported a reduction in symptomatology, while a second case study reported no improvement. In schizophrenia, an open-label study in female patients (n = 10) reported reduced symptoms after 2 weeks of KD, a single case study reported no improvement. In a brief report, 3 weeks of KD in a mouse model normalized pathological behaviors. In ASD, an open-label study in children (n = 30) reported no significant improvement; one case study reported a pronounced and sustained response to KD. In ASD, in four controlled animal studies, KD significantly reduced ASD-related behaviors in mice and rats. In ADHD, in one controlled trial of KD in dogs with comorbid epilepsy, both conditions significantly improved.

Conclusion: Despite its long history in neurology, the role of KD in mental disorders is unclear. Half of the published studies are based on animal models of mental disorders with limited generalizability to the analog conditions in humans. The review lists some major limitations including the lack of measuring ketone levels in four studies and the issue of compliance to the rigid diet in humans. Currently, there is insufficient evidence for the use of KD in mental disorders, and it is not a recommended treatment option. Future research should include long-term, prospective, randomized, placebo-controlled crossover dietary trials to examine the effect of KD in various mental disorders.

Keywords: ketogenic diet, psychiatry, mental disorders, ketones, epilepsy

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INTRODUCTION

The ketogenic diet (KD) has a long-standing place in neurology and has been used for treatment-resistant epilepsy since the 1920s (1). KD consists of a rigidly controlled high-fat, low-protein, and low-carbohydrate diet usually with a 4:1 lipid:non-lipid ratio (fat to protein and carbohydrate ratio) (2). Woodyatt noted that in a normal person in a state of starvation or eating a diet containing low carbohydrate and a high percentage of fat, the ketones acetone, acetoacetate, and beta-hydroxybutyric acid increase (3), and the absence of glucose serves as alternative fuels for the body. KD has been proven an effective treatment in difficult-to-control seizures with its use primarily in children with epilepsy (4, 5), particularly those with epileptic encephalopathies whereby epileptic activity may contribute to severe neurological and cognitive impairments (6). The finding that KD is beneficial for epilepsy was supported by a systematic review (7), meta-analysis (8), and a Cochrane review (9). KD and related diets have been proven useful in pharmacoresistant childhood epilepsy (10).

The mechanism by which KD acts is not clearly understood. However, among the many hypotheses advanced, elevation of brain acetone may account for the efficacy of the diet in epilepsy as it has proven anticonvulsant effects (11). In a variation of the diet, the medium-chain triglyceride (MCT) KD increases plasma levels of decanoic acid, which *in vivo* has been shown to be anticonvulsant; although the precise mechanism remains unclear (12). In young and adult rats, KD increases concentrations of kynurenic acid (KYNA) in the hippocampus and striatum but not the cortex (13). Elevated levels of KYNA in the cerebrospinal fluid have been demonstrated in patients with schizophrenia (14) and bipolar disorder (15). Pharmacological manipulation of kynurenines is a potential treatment strategy for psychiatric disorders (16).

Currently, there are no international protocols guiding the implementation of the diet, rather dietary recommendations are based on individual treating physician's advice. Consequently, there exists a need for more standardized protocols for management recommendations for clinical and research use (17). In 2006, a group of 26 pediatric epileptologists and dieticians was convened to create a consensus statement regarding the clinical management of KD. They specified the following absolute contraindications to commencing KD "carnitine deficiency (primary), carnitine palmitoyltransferase (CPT) I or II deficiency, carnitine translocase deficiency, beta-oxidation deficiencies including medium-chain acyl dehydrogenase deficiency (MCAD), long-chain acyl dehydrogenase deficiency (LCAD), short-chain acyl dehydrogenase deficiency (SCAD), long-chain 3-hydroxyacl-CoA deficiency, medium-chain 3-hydroxyacl-CoA deficiency, pyruvate carboxylase deficiency and porphyria. Relative contraindications of KD include the following: inability to maintain adequate nutrition, surgical focus identified by neuroimaging and video EEG monitoring, and parent or caregiver non-compliance" (18). The possible risks of KD must be weighted against its potential value for seizure control or its other benefits (19).

Ketogenic diet has been assessed in a variety of neurological conditions other than epilepsy in both animal models and human trials. In an animal model of amyotrophic lateral sclerosis, SOD1-G93A transgenic mice were fed KD. It was shown that KD led to significant alterations in the clinical manifestation of the disease, specifically a higher motor neuron count in the lumbar spinal cord and preserved motor function (20). KD has also been trialed in rats following controlled cortical impact injury, a model for brain trauma, showing that the diet improves both cognitive and motor functioning (21). In an animal model of multiple sclerosis, the effects of KD on memory impairments and inflammation expressed by experimental autoimmune encephalomyelitis were examined. In mice, it was demonstrated that brain inflammation was associated with impaired spatial learning and memory function, and the administration of KD exerted protective effects against these. The proposed mode of action was through attenuation of the immune response and increased oxidative stress observed in the mice (22).

In humans, KD has been trialed in a number of neurological conditions. In a randomized, double-blind, placebo-controlled, parallel group study in Alzheimer's disease, an oral ketogenic compound AC-1202 was tested on 152 patients. Regular medications were continued throughout the study. Daily dosing of AC-1202 significantly elevated the levels of beta-hydroxybutyrate 2 h after administration. After 45 and 90 days, patients treated with AC-1202 had significant improvements on the ADAS-Cog scale (23). In a small study of seven patients with Parkinson's disease, five adhered to KD for 28 days (24). Scores on the Unified Parkinson's Disease Rating Scale improved in all five as did symptoms such as resting tremor, freezing, balance, gait, mood, and energy levels. These results should be interpreted with caution due to the small sample size, subjective ratings, and the lack of a control group to exclude a placebo effect. The modified Atkins diet (a high-fat, low-carbohydrate diet), which creates a ketotic state was trialed in adolescent patients with chronic daily headaches (25). Due to difficulties adhering to the diet, the study was terminated prematurely. Three participants reported an improvement in headache severity and quality of life; however, they still required pharmacotherapy to manage their condition. In a comprehensive review of KD in diverse neurological conditions, Stafstrom and Rho concluded that there are rich opportunities for further investigation of KD in both the laboratory and clinical practice (26).

The therapeutic advantage of KD has been replicated in animal models of neurological illnesses, and the purported underlying mechanisms include those which improve mitochondrial function (27). Molecular, biochemical, and physiological studies tend to support the assumption that cellular energy status is a determinant for multiple disorders (28). Aberrant energy production has been associated with cancer (29), heart failure (30), aging (31), and neurological conditions such as epilepsy (32) and Alzheimer's disease (33). The precise pathways by which energy disruption is related to these and other disorders are unknown. There are also strong indications of metabolic pathways involving energy production in the pathophysiology of some mental disorders including bipolar disorder, depression, schizophrenia (34) autism spectrum disorder (ASD) (35), and potentially attention deficit hyperactivity disorder (ADHD) (36). There is also a recognized comorbidity between epilepsy and mental disorders (37), which might indicate some commonality of mechanisms.

Given the degree of interest in KD and neurological conditions, the aim of this narrative review is to examine the effect of the diet in mental disorders. The literature searched in anxiety, depression, bipolar disorder, schizophrenia, ASD, and ADHD.

METHOD

A comprehensive search of the electronic databases PubMed, PsychINFO, and Scopus for peer-reviewed articles published in English was conducted in the last week of November 2016 and updated in January 2017. Search terms were "bipolar disorder" "manic depress*" "depress*" "schizophren*" "autism" "ASD" "attention deficit hyperactivity disorder" "ADHD" "obsessive compulsive disorder" "OCD" "anxiety" "anxi*" "psychiatry" "mental disorder*" (group 1) AND "ketogenic diet" "ketosis" "ketogenesis" "ketone bodies" "high fat low carbohydrate" "diet" "acetone" "acetoacetic acid" "beta-hydroxybutyric acid" "acetyl-coA" "ketonemia" "ketonuria" "fatty acid metabolism" "hyperketonemia" "fasting" "nutritional ketosis" "acidotic" (group 2). These terms were combined as follows: group 1 AND group 2. In addition, a hand-search of the reference lists of published articles was also conducted, and articles were assessed for their suitability in the review. An initial search was conducted using all the search terms listed above, and abstracts were reviewed by author Emmanuelle C. S. Bostock. Full text publications were retrieved for those that addressed the subject matter.

RESULTS

The results are discussed by mental disorders examining animal and human studies including case reports and studies of patient groups. The search yielded 15 studies that examined KD in mental disorders, specifically anxiety, depression, bipolar disorder, schizophrenia, autism, and, ADHD. These studies included nine animal models, and in humans four case studies and two uncontrolled trials. A summary of results by animal models and human studies are presented in **Tables 1** and **2**, respectively.

Anxiety

Anxiety is a common mental disorder affecting 18.1% of the population in the United States (52). In humans, functional magnetic resonance imaging indicates that anxiety is associated with activation in the ventromedial prefrontal cortex and hippocampal regions of the brain (53). Symptoms of anxiety and disorders are more frequent in patients with epilepsy with one recent study reporting a lifetime incidence of 22.8% as opposed to 11.2% in people without epilepsy (54).

In a recent animal model study of anxiety in male rats, two methods of administration of exogenous ketone supplement were applied (38). In the chronic administration condition, 48 male Sprague-Dawley (SPD) rats were fed for 83 days with either a standard diet ($n = 9$) or standard diet plus one of four ketone supplementation conditions. In the sub-chronic intragastric gavage bolus condition, 39 SPD rats were fed with standard diet and gavaged daily with water (control, $n = 11$) or 1 of 3 levels of ketone supplementation for 7 days; this was repeated with 32 Wistar Albino Glaxo/Rijswijk rats receiving a half-dose of supplementation. In both modes of supplementation, beta-hydroxybutyrate was significantly elevated indicating ketosis. All treatment conditions resulted in reduced anxiety as assessed by behavior on the elevated plus maze. The dependent variables of less entries and time spent in closed arms, more entries and time spent in open arms, more distance traveled in open arms, and delayed entry to closed arm were used as an analog of anxiety in humans. The authors hypothesized that the mode of action was through the glutamatergic and/or GABAergic and purinergic systems.

Depression

In a recent review, a number of studies suggested that depression is associated with an increased risk of epilepsy (55). The effectiveness of conventional antidepressant therapies is frequently examined in animals. In rodents, to test current levels of depression, a methodology known as the Porsolt forced swim test is often employed (56) and has been used in testing the effectiveness of new antidepressant drugs (57). In the two-part swim test, animals are first placed in a container from which they cannot escape. When they then stop trying and immobility ensues, a state of behavioral despair is shown. Second, to assess the effects of antidepressants, the time spent immobile is used as a dependent variable, and reductions are interpreted for significance (56). To examine the antidepressant properties of KD, 20 Wistar rats given the diet (4:1 lipid:non-lipid ratio) were compared to 20 fed a standard diet (39). It was found that rats on KD spent less time immobile than control rats thus providing some evidence for potential antidepressant effects of the diet. The diet duration was 7 days, and levels of beta-hydroxybutyrate were measured.

Brain morphology and behavior of CD-1 mice exposed to KD (4:1 lipid:non-lipid ratio) for 30 days *in utero* and fed a standard diet in postnatal life were examined (40). Adult mice that were fed the diet *in utero* showed reduced susceptibility to anxiety and depression and exhibited elevated physical activity when compared with control mice fed a standard diet *in utero*. Morphological differences included cerebellar volumetric enlargement by 4.8%, a hypothalamic reduction by 1.39%, and a corpus callosum reduction by 4.77%, as computed relative to total brain volume.

While animal models pave the way for future research in humans, the conclusions that may be made are limited. The mechanism by which KD acts in animal models of depression is unknown; however, in children with epilepsy, KD resulted in significant alterations in levels of serotonin and dopamine neurotransmitters (58), both of which are implicated in anxiety and depression. To the best of our knowledge, there are no studies examining the effects of KD in depressed humans.

Bipolar Disorder

A diagnosis of bipolar disorder type I requires an episode of mania, which consists of "a distinct period of abnormally and persistently elevated, expansive or irritable mood, lasting at least 1 week (or any duration if hospitalization is necessary)" (59). A diagnosis of bipolar disorder type II requires at least one episode of hypomania. In a study of nutrition and exercise behavior, when compared to patients with schizophrenia or healthy controls, it

TABLE 1 | Summary of findings in animal models.

Reference	Condition	Subjects (*n*)	Mode of administration of diet	Duration of diet	Ketone*	Result
(38)	ANX	Sprague-Dawley (48) and Wistar Albino Glaxo/Rijswijk rats (32)	Exogenous ketone supplement	83 or 7 days *via* oral gavage	✓	Reduced ANX-related behavior
(39)	DEP	Wistar rats (20)	4:1 lipid:non-lipid ratio	7 days	✓	Some evidence for potential antidepressant properties
(40)	DEP	CD-1 mice (20)	4:1 lipid:non-lipid ratio *in utero* and SD in postnatal life	30 days	✓	Those fed KD *in utero* showed reduced susceptibility to ANX and depression and increased hyperactivity
(41)	SZ	C57Bl/6 mice (?)	77.6% fat, 9.5% protein, and 4.7% crude fiber, AD fiber 4.7%	3 weeks	✓	Normalized pathological behaviors including psychomotor hyperactivity, stereotyped behavior, social withdrawal, and working memory deficits
(42)	ASD	Swiss mice (16)	(Lard 690 g/kg, sunflower oil 5 g/kg, protein 250 g/kg, fiber 10 g/kg, ash 5 g/kg)	*In utero* exposure to KD (70 days)	–	Statistically significant social deficits and stereotypies that are common behaviors in those with ASD
(43)	ASD	Wistar rats (6)	6:1 lipid:non-lipid ratio	10–14 days	✓	KD had a significant effect and was able to modify complex social behaviors in valproic acid and control rats
(44)	ASD	BTBR mice (?)	6.3:1 lipid:non-lipid ratio	14 days	✓	Temporal cortex and hippocampus brain regions showed improvements on autistic deficits associated with myelin formation and white matter development
(45)	ASD	EL mice (?)	3.0:1 or 6.6:1 lipid:non-lipid ratio	3–4 weeks	✓	Social novelty test—females fed higher KD ratio exhibited significant preference to the new mouse. Self-grooming significantly decreased in males
(36)	ADHD	Dogs (21)	10% moisture, 28% protein, 15% fat, 6% ash, 2% crude fiber, and MCT oil	6 months	✓	Significant improvement in ADHD-related behaviors

*ANX, anxiety; DEP, depression; BD, bipolar disorder; SZ, schizophrenia; *, ketone levels reported; ?, unknown sample size; MCT, medium-chain triglyceride; ASD, autism spectrum disorder; ADHD, attention deficit hyperactivity disorder; KD, ketogenic diet.*

TABLE 2 | Summary of findings in human studies.

Reference	Condition	Subjects (*n*)	Mode of administration of diet	Duration of diet	Ketone*	Result
(46)	BD	Human women (2)	Ratio not mentioned in first but in second (70% fat, 22% protein, and 8% carbohydrate)	2 and 3 years	✓	Mood stabilization
(47)	BD	Human woman (1)	4:1 lipid:non-lipid ratio	1 month	No urinary ketones detected	No clinical improvement
(48)	SZ	Human women (10)	Not listed	2 weeks	Not listed	Statistically significant decrease in symptomatology
(49)	SZ	Human woman (1)	Not listed	12 months	Not listed	No recurrence of auditory or visual hallucinations
(50)	ASD	Human children (30)	30% MCT, 30% fresh cream, 11% saturated fat, 19% carbohydrate, and 10% protein	6 months (intervals of 4 weeks with 2 diet-free weeks)	✓	40% non-compliance. Two children showed significant improvements on Childhood Autism Rating Scale, while the rest showed mild-to-moderate improvements
(51)	ASD	Human child (1)	1.5:1 lipid:non-lipid ratio	Several years	✓	Score on the Childhood Autism Rating Scale decreased from 49 to 17 (severe autism to non-autistic)

*DEP, depression; BD, bipolar disorder; SZ, schizophrenia; *, ketone levels reported; MCT, medium-chain triglyceride; ASD, autism spectrum disorder.*

was found that patients with bipolar disorder were more likely to report risk factors for poor nutrition including difficulty obtaining or cooking food (60). Treatments for bipolar disorder typically include an antipsychotic and a mood stabilizer, and many patients are treated with adjunct anticonvulsants.

In a case study of two women with bipolar disorder type II, the patients maintained ketosis for an extended period of 2 and 3 years, respectively. The women reported subjective mood stabilization, which exceeded that of medication as well as an overall improvement in their condition that they related to ketosis (measured in the urine). Both women tolerated the diet well with few or no side effects reported (46). The ratio of KD was not mentioned in the first case, but in the second it was estimated to be around 70% fat, 22% protein, and 8% carbohydrates.

In a separate case study, a woman with treatment-resistant bipolar disorder was placed on KD (4:1 lipid:non-lipid ratio) and showed no clinical improvement (47). It should be noted that no urinary ketones were detected, the type of bipolar disorder was not listed (type I or type II), and treatment duration limited to 1 month.

These studies illustrate that careful attention should be paid to the intricacies of the diet (such as measuring ketones and calculating macronutrient ratios) to fully examine its efficacy in bipolar disorder, as well as the need for larger well-designed placebo-controlled studies in this area. The mechanism by which KD may be effective in bipolar disorder is based on the hypothesis that acidosis achieved through ketosis reduces intracellular sodium and calcium, both of which are elevated in the disorder (47). Mood stabilizers reduce intracellular sodium in an activity-dependent manner within the context of KD; this is hypothesized as being achieved through the acidification of the blood (46).

Schizophrenia

Schizophrenia is associated with high levels of morbidity. The precise pathophysiology of the disorder is unknown, and current pharmacological treatment options are limited (61). Animal models of schizophrenia fit into four induction methods including developmental, drug-induced, lesional, or genetic manipulation (62). In a recent drug-induced (MK-801, dizocilpine) animal model of schizophrenia in C57BL/6 mice, it was demonstrated that 3 weeks of KD (77.6% fat, 9.5% protein, and 4.7% crude fiber, AD fiber 4.7%) normalized pathological behaviors (41). These included psychomotor hyperactivity, stereotyped behavior, social withdrawal, and working memory deficits, which reflect the positive, negative, and cognitive symptoms of the disorder. Weight loss was an observed side effect. Elevated levels of the ketone beta-hydroxybutyrate and decreased glucose levels indicated that metabolic adaptation had occurred.

In a 1965 study, the effect of KD was tested in 10 female patients with schizophrenia. All participants were reported to have a poor prognosis and were not treatment responsive at the time. Concurrent therapies remained throughout the duration of the diet including pharmacotherapy and electroconvulsive therapy. The Beckomberga Rating Scale was administered to patients three times during the diet period (2 days, 2 weeks, and 1 week after discontinuation), there was a statistically significant decrease in symptomatology after 2 weeks of established KD (48). This was, however, a small, poorly controlled study, and in addition, the lipid:non-lipid ratios were not detailed, and it was not stated whether ketone levels were measured throughout the study. A further consideration is that the study was conducted in 1965 before the advent of atypical antipsychotics and their metabolic side effects.

In a case study of a 70-year-old overweight woman with a diagnosis of schizophrenia, KD was initiated by her treating physician (49). The patient remained on KD for 12 months and reportedly had no recurrences of auditory or visual hallucinations, and the patient lost weight. The patient reported eating mainly lean proteins and low-carbohydrate vegetables (the lipid:non-lipid ratio was not listed), ketosis was not confirmed and perhaps not established due to the lack of dietary fats listed; therefore, this case report is of indeterminate value.

Some studies suggest that abnormal glucose and energy metabolism may underlie the pathophysiology of schizophrenia, which may provide some potential pointers into the hypothesized mode of action of KD in the disorder (63, 64). Others have noted that abnormal glucose metabolism may occur secondary to antipsychotic medications alongside significant treatment side effects such as weight gain, hyperglycemia, and diabetes (65). The high metabolic risk associated with schizophrenia is due to genetic and environmental factors (66).

Autism Spectrum Disorder

Features of patients with ASD include compromised social interaction and communication (67). It is estimated that between 5 and 40% of patients with autism will develop epilepsy (68), and while most patients will respond to pharmacotherapy, in one study, 34% of 170 patients had medically refractory epilepsy (69). The precise pathogenesis of ASD remains unknown, but genetic and environmental factors have been known to contribute to its onset. One such factor is exposure to valproic acid (VPA) *in utero*, which is associated with a 12% incidence of ASD in children (70) and is used as an animal model of induction of ASD (42).

Using the animal model of autism induced by prenatal exposure to VPA in mice, the effects of KD were examined. Pregnant Swiss mice received a single intraperitoneal injection of 600 mg/kg of VPA ($n = 26$) or saline ($n = 18$) on gestational day 11. At day 21, 16 VPA treated and 16 control mice were used. Half of each group was fed KD (lard 690 g/kg, sunflower oil 5 g/kg, protein 250 g/kg, fiber 10 g/kg, ash 5 g/kg), while the other received a standard diet. Ketone levels were not measured. After 70 days on KD, a statistically significant result was found in mice with VPA in behaviors such as social deficits and stereotypies that are common behaviors in those with ASD (42). It is also believed that mitochondrial dysfunction may play a role in the onset of ASD (35). Ahn et al. (43) aimed to determine if KD could reverse the social deficits and mitochondrial dysfunction seen in a prenatal VPA animal model of autism using Wistar rats. On postnatal day 21, rats were placed on either KD (6:1 lipid:non-lipid ratio) or standard diet for 10–14 days. Beta-hydroxybutyrate was measured. KD had a significant effect and was able to modify complex social behaviors in VPA and control rats and mitochondrial respiration (43).

Another animal model of autism using the inbred BTBR mouse strain that exhibits three core features of autism, including reduced sociability, communication, and increased repetitive behavior, was studied (71). In another study, 33 genes were differentially expressed in the temporal cortex and 48 in the hippocampus suggesting deficits in the stress response and in neuronal signaling and communication in BTBR mice. After 14 days on KD (6.3:1 lipid:non-lipid ratio), both brain regions showed improvements on autistic deficits associated with myelin formation and white matter development (44). One study has found that in BTBR mice, KD reduces total gut microbial and compositional remodeling of the mouse microbiome providing a potential explanation as to its efficacy in this model (72).

In an animal model with behavioral characteristics of ASD and comorbid epilepsy in male and female EL mice, the effect of KD was assessed (45). Testing occurred at 8–9 weeks postpartum following 3–4 weeks of dietary treatment. Animals were fed either a standard diet or one of two KDs (3.0:1 or 6.6:1 lipid:non-lipid ratio). KD raised ketones in all groups, but the higher fat ratio deepened ketosis. Both KDs significantly increased sociability, time spent in the chamber with another mouse, in females and males. Social novelty, preference for a newly introduced mouse was higher in females fed the higher KD ratio. The test of repetitive behavior (self-grooming) was significantly decreased in males but was non-significant in females. This study provides some intriguing results regarding the effects of sex and KD in a mouse model of ASD and idiopathic epilepsy.

The role of KD in ASD has been examined in a pilot study of 30 children (50). The diet (30% of energy as MCT oil, 30% fresh cream, 11% as saturated fat, 19% carbohydrates, and 10% as protein) was administered for 6 months with intervals of 4 weeks with 2 diet-free weeks. Of the total sample, 40% did not comply or did not tolerate the diet. Urinary ketones were measured. In the remaining sample, two children showed significant improvements on the Childhood Autism Rating Scale, while the rest showed mild-to-moderate improvements. As observed in patients with epilepsy, after the termination of KD the benefits persisted, which raise intriguing questions regarding the effects of plasticity.

In a case study of a child with autism and epilepsy, following standard treatment non-response, the individual was placed on KD (1.5:1 lipid:non-lipid ratio) with adjunct anticonvulsant therapy (51). The patient was in ketosis. After initiation of the diet several benefits ensued including the resolution of morbid obesity and the improvement of cognitive and behavioral features of the disorder. After several years on the diet, the patient's score on the Childhood Autism Rating Scale decreased from 49 to 17, a change from a rating of severe autism to non-autistic, and IQ increased by 70 points. Fourteen months following the initiation of the diet the patient was also seizure free.

The suggested mechanisms of action of KD in ASD include that it may reduce pain sensitivity through the reduction of glucose and may have anti-inflammatory properties as it reduces swelling and plasma extravasation (42). In a systematic review of KD in ASD it was concluded that the limited number of reports of improvements after treatment with the diet is not sufficient to attest to the practicability of KD as a treatment for the disorder (73).

Attention Deficit Hyperactivity Disorder

Attention deficit hyperactivity disorder is characterized by a lack of behavioral inhibition and by neuropsychological deficits in four areas, including working memory, self-regulation of affect–motivation–arousal, internalization of speech, and behavioral analysis and synthesis (74). ADHD is the most commonly occurring mental disorder in children and adolescents with epilepsy occurring in 16 (29.1%) of 78 patients (75). Children with ADHD have a high frequency of epileptiform discharges as observed by EEG (76). In a prospective study of children with epilepsy ($n = 34$) on KD it was found that after 1 year on the diet there was a statistically significant improvement of attention and social functioning (77).

There is little evidence examining ADHD and KD, but a 6-month prospective, randomized, double-blinded, placebo-controlled, crossover dietary trial compared the effects of KD (10% moisture, 28% protein, 15% fat, 6% ash, 2% crude fiber, and MCT oil) or a standard diet on behavior in 21 dogs with comorbid ADHD and idiopathic epilepsy (36). It was hypothesized that there were three specific behaviors related to ADHD in dogs including excitability, chasing, and trainability. ADHD in dogs is manifested as inattention and excitability/impulsivity, which have been likened to the disorder in humans (78). When compared with the standard diet, KD resulted in a significant improvement in ADHD-related behaviors. Serum beta-hydroxybutyrate was measured. The mechanisms of behavioral improvements during KD remain unknown. The authors postulated that alterations of energy metabolism in the brain may contribute to behavioral changes. Research into humans with ADHD and KD is lacking.

DISCUSSION

In neurology, KD is an established treatment option for treatment-resistant epilepsy with evidence from a range of studies including controlled trials. By contrast, KD research in humans with mental disorders, though extending over a 50-year period, has received little attention with few studies other than case reports, small sample size open studies, and no controlled trials. Animal studies have been more systematic, investigating mechanisms as well as outcomes on putative disease analogs in rodents and canines, the latter including randomized controlled trials of KD.

With respect to mechanisms, the pathophysiology of the mental disorders covered in this review is not clearly understood, though impaired metabolism due to mitochondrial dysfunction has been identified as an important substrate (34). This is congruent with findings in neurological conditions, Stafstrom and Rho concluding that energy metabolism changes induced by KD in neurological conditions suggest a final common pathway implicating mitochondrial function (26). KD may also influence neuronal plasticity by modifying neural circuits and cellular properties to normalize function (26). Mitochondrial dysfunction may be relevant in some mental disorders including schizophrenia, ASD, and ADHD, whereas the improvements seen in anxiety, depression, and bipolar disorder may be related to alterations of neurotransmitters.

One other possible mediator of the beneficial effects of KD in mental disorders is the effect on sleep. In a study of 18 children with treatment-resistant epilepsy, after 3 months of KD sleep was reported to be enhanced with a pattern of significant reduction in total night sleep, preservation of slow-wave sleep, increased rapid eye movement (REM) sleep, and decrease in sleep stage 2 (79). The mechanisms by which KD affects sleep is unclear (80), and more studies are necessary to confirm reports that certain dietary patterns and foods improve sleep (81).

Sleep problems and mental disorders are codependent conditions that exacerbate each other and lead to impaired quality of life and increased disability (82). Impairments of sleep are a widespread feature of mental disorders. Anxious patients have been found to have significantly less sleep period time, total sleep time, percentage stage REM and percent stage 4 sleep, shorter latency to stage REM, and greater percent stage 1 sleep than healthy controls (83). REM sleep abnormalities including shortening of REM latency, lengthening of the duration of the first REM period, and heightening of REM density are found in patients with depression (84). In patients with inter-episode bipolar disorder, shorter sleep onset latency and increased REM density has been observed (85). A decrease of REM sleep latency in schizophrenia has been described (86). Individuals with ASD have prolonged sleep latency, more frequent nocturnal awakenings, lower sleep efficiency, increased duration of NREM stage 1 sleep, and decreased deeper stages of NREM sleep (87). In ADHD, disturbed sleep architecture has been described including shorter REM latencies, reduced REM sleep, and increased delta sleep percentage (88). It should also be noted that sleep deprivation can precipitate mania in bipolar disorder and seizures in epilepsy (89) and can be used as a treatment for depression (90). The specific effects of KD on these mental disorder-related sleep symptoms has not been studied in detail, but interactions are likely and may be possible mediators of a therapeutic effect.

In epilepsy, KD acts differently to antiepileptic drugs (AED) in seizure prevention. While AED act directly on ion channels and synaptic processes, KD acts through intermediary metabolic pathways (91). Chang et al. showed that an MCT (palm oil and coconut oil) diet, a variation of KD, reduces seizures in children *via* inhibition on AMPA receptors (12, 92, 93). The questions posed by the literature indicate that the mechanism of action is still unknown, and there may be many potential pathways involved. The mechanism of action appears different from AED and therefore probably psychiatric drugs also, which opens potential avenues for treatment in a manner that may supplement conventional pharmacological treatment approaches. The exact mechanism of action of KD is unclear, and for detailed discussion, see Rogawski et al. (91). Thus, present knowledge indicates that KD exerts its effects on seizure control by mechanisms different from conventional AED and therefore, in psychiatry, this may also be the case although as yet unproven.

There are a number of reasons why the effectiveness of KD in mental disorders remains unproven. In addition to the low number of human studies, the quality of the studies has some significant limitations. Sample sizes are small, there is no control for placebo effects, and the establishment of ketosis is generally lacking with no confirmatory measurement of ketones in three human studies. There are also significant limitations associated with the diet itself including the detailed regimen, unpalatable food choices, side effects, and duration of diet required. There are also no enforced standards as to what constitutes KD in humans with variable lipid:non-lipid ratios reported. KD monotherapy is used in animal models of mental disorders but remains unexamined in human studies. Ten adult patients with epilepsy followed KD monotherapy, and it was concluded that it may be feasible, well tolerated, and an effective long-term alternative (94).

To comply with KD, patients who may be acutely unwell are required to measure food portions to ensure that the macronutrient targets associated with the diet are met, and they may find it difficult to adhere to such a demanding diet (47). This is particularly so for patients with mental disorders where symptoms such as impulsivity in mania, apathy, and reduced appetite in depression, food cravings, and binge eating associated with antipsychotic medications may variously interfere with compliance with KD (95). A mitigating factor to the outcomes in children with epilepsy may be that the diet is typically administered in a hospital setting initially and subsequently, by caregivers.

El-Mallakh and Paskitti have outlined the adverse consequences of KD including constipation, menstrual irregularities, elevated serum cholesterol and triglycerides, hypoproteinemia, hemolytic anemia, elevated liver enzymes, and gall stones (96). Kidney stones have been noted to occur in 1 of 20 children on the diet (97). In a period of almost 2 years, prospective monitoring of 52 children with pediatric epilepsy was conducted. Ten percent of children experienced serious adverse events associated with the diet 1 month after initiation (98). This included presacral and periorbital edema, developmental impairment, and unwanted weight loss in an infant, renal tubular acidosis, viral gastroenteritis, abnormal liver function, and thrombocytopenia. It should be noted that all patients were being treated with concomitant VPA. It was reported in a retrospective study of 158 children with intractable epilepsy that, in 80% emesis, food refusal and hypoglycemia occurred (99).

By definition, KD is confirmed by the production of ketones measured in the blood or urine. In the reviewed literature covering KD in mental disorders, four studies did not report ketone levels, which severely limit comparability across studies and the ability to invoke any consistent mechanism. One study compared whether measuring serum beta-hydroxybutyrate or urinary ketones was superior to monitor KD (100). In humans, it was found that beta-hydroxybutyrate correlated more strongly with a reduction in seizures than urinary ketones; therefore, future studies should measure ketones in the blood. Another issue is that the lipid:non-lipid ratios used were different (see **Tables 1** and **2**). In a study that compared the efficacy and tolerability of the 3:1 versus the 4:1 lipid:non-lipid ratios, the latter was shown to have a higher seizure-free outcome (2).

One issue when interpreting the results is the levels of evidence in the evidence-based hierarchy. Animal models of mental disorders are considered valuable preclinical tools to investigate the neurobiological basis of a disorder (62). While this may be true, they are nonetheless subject to a number of limitations. One such limitation is the issue of validity, and their use is based on the assumption that humans and animals share basic neurobiological

mechanisms associated with the complex behaviors that mimic mental disorders in animals (101).

Another difficulty posed to practitioners is that there are currently no international protocols guiding the administration of the diet; this is something that may be established from future research into KD. There was only one case study that detailed what the participant, diagnosed with schizophrenia, ate, and it was not established whether this individual was in ketosis. In the various studies in humans, outcomes were assessed following dietary durations that varied from 7 days to 2 years.

Further research into the neural correlates of KD is needed to help explain the mechanisms by which it acts. Some suggestions regarding methodologies, provided by Fusar-Poli are elaborated below. Changes in glucose metabolism seen in KD could be examined using positron emission tomography fluorodeoxyglucose. To observe the neural correlates of KD, a combination of electrophysiological measures including EEG and magnetoencephalogram and fMRI/PET to combine the high temporal resolution of the former with the high spatial resolution of the latter may be used (102).

In the neurological literature, a single study, in Alzheimer's disease, used a synthesized ketogenic compound AC-1202 rather than a KD. AC-1202 is an MCT composed of glycerine and caprylic acid (23). It is not yet clear what role ketogenic pharmacotherapy options might play alongside or as a substitute for KD.

While these animal studies are placing research into KD on a firm footing and identifying some promising leads, on balance the evidence in humans is insufficient to form an opinion as to the efficacy or lack thereof of this intervention in the mental disorders reported. Further basic research to clarify the specifics of dietary manipulation or supplementation required to produce optimum ketosis in specific models is an obvious intermediate step toward studying the effectiveness of the diet in human mental disorders using conventional phases of research including open-label studies and randomized controlled trials.

AUTHOR CONTRIBUTIONS

EB derived the concept of the article from which she received supervision and expert advice in the area of psychiatry from KK and neurology from BT.

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Chapter 5

Mania Associated With Herbal Medicines, Other Than Cannabis: A Systematic Review and Quality Assessment of Case Reports

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Mania Associated With Herbal Medicines, Other Than Cannabis: A Systematic Review and Quality Assessment of Case Reports

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Background: DSM-5 introduced the diagnostic category of substance/medication-induced bipolar and related disorder. This systematic review examines published reports linking mania with the consumption of herbal medicines (HM), excluding cannabis. Putative pathophysiological mechanisms that may account for the reported HM being associated with mania are discussed.

Methods: A systematic search of EMBASE, CINAHL, Health Source, PsychINFO, and PubMed. The quality of case reports meeting inclusion criteria was assessed using the modified Quality Assessment Scale by Agbabiaka.

Results: Nineteen single and seven multiple-case reports met inclusion criteria. These yielded a study sample of 35 case reports, 28 of herbal medicine associated mania, 5 of hypomania, and two mixed states, in 17 females [age in years M(SD) = 43.1(13.2)] and 18 males [40.7(18.1)]. A total of 11 herbal medicines were implicated. Case reports by herbal medicine (number of reports) comprised: St John's wort (*Hypericum perforatum)* (14); Ginseng (*Panax ginseng*) (5); brindleberry (*Garcinia cambogia*) (4); ma-huang (*Ephedra sinica*) (3); "herbal slimming pills" (2); Herbalife products (2); Hydroxycut (1); horny goat weed (*Epimedium grandiflorum*) (1); "herbal body tonic" (1); celery root (*Apium graveolans*) (1), and a "herbal mixture" (1). All case reports were associated with use rather than withdrawal of herbal medicines. Only one case report was rated for probability of association using a standardized algorithm. Laboratory assays to confirm composition of the herbal preparation were reported in only one article describing two cases and indicating admixture of a likely causal pharmaceutical in the herbal preparation.

Conclusions: Causal attributions are problematic given the limited number of reports, antidepressant co-prescribing in 7 cases, insufficient data regarding pattern and type of herbal medicine use, and lack of a reference frequency for spontaneous mania.The quality assessment scores across the 26 papers (35 case reports) were as follows: low quality (0), lower-medium quality (9), upper-medium quality (10) and high quality (7). Putative pathophysiological mechanisms were postulated for nine of the 11 herbal medicines and centered on HPA-axis activation and increased monoamine activity.

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Systematic study of the association between herbal medicines and the course of bipolar disorder may contribute to defining targets for pathophysiological research.

Keywords: herbal medicine, case report, bipolar disorder, mania, phytotherapy

INTRODUCTION

DSM-5 introduced the diagnostic category of "substance/medication-induced bipolar and related disorder." This diagnosis requires a temporal association between occurrence of mania and the use or withdrawal of substances or medications. The precipitating agents may include intoxicating drugs such as cannabis or amphetamines, prescribed medications for mood disorders such as antidepressants, prescribed medications for other illnesses such as steroids, and herbal medicines (HM). DSM-5 sets a less restrictive standard for the diagnosis of substance/medication-induced bipolar and related disorder than for mania. Criterion A for mania, as required for a diagnosis of bipolar disorder, is "A distinct period of abnormally and persistently elevated, expansive, or irritable mood and abnormally and persistently increased activity or energy, lasting at least 1 week and present most of the day, nearly every day (or any duration if hospitalization is necessary)" (1). This compares with criterion A for substance/medication-induced bipolar and related disorder "a prominent and persistant disturbance in mood that predominates in the clinical picture and is characterized by elevated, expansive or irritable mood."

The concept of substance/medication-induced mania antedates the DSM-5 classification, for example it was denoted as bipolar disorder-III in Akiskal's classification of bipolar spectrum disorders (2). Mania associated with the antidepressant medication imipramine was reported by Ball and Kiloh (3) and mania has also been associated with lithium withdrawal (4). The first reported association of mania with a HM was in 1984 by Price et al. who explored the relation of yohimbine, an α-2 adrenergic receptor antagonist, to mania under experimental conditions (5). A number of substances have beneficial effects in bipolar disorder and are prescribed medications in routine treatment of mania for example lithium, sodium valproate and atypical antipsychotics, and in bipolar depression for example lithium, lamotrigine, atypical antipsychotics and selective serotonin reuptake inhibitors (6). Their precise mechanism of action is not fully understood, reflecting a lack of understanding of the pathophysiology of mania and depression. The study of substance/medication-induced bipolar and related disorder, notwithstanding limitations of causal attributions, may further our understanding of brain mechanisms relevant to the occurrence and course of bipolar disorder. This is particularly so for mania which has a strikingly unique set of clinical features, is often of abrupt onset and has a relatively short duration with a median of 13 weeks (7).

Many conventional drugs originate from plant sources (8). HM or phytotherapy refers to the use of plant-based medicinal preparations, a subset of complementary and alternative medicines (CAM). In the United States, HM are regulated as food products and therefore are not subject to the phases of clinical testing that pharmaceuticals must undergo prior to market release. Manufacturing standards are in keeping with those applicable to other foods (9), the strength and composition of HM may therefore vary widely.

According to survey data, the use of CAM is prevalent and increasing throughout many Western countries (10–12). CAM usage is common in persons with psychiatric illness. In a survey of CAM usage among psychiatric inpatients ($n = 82$) it was found that 63% used at least one CAM modality within the previous 12 months, including 44% who used HM (13). This may be attributed in part to factors such as side effects of conventional medicines, ready access without prescription, a belief that HM cause no harm, and in the case of bipolar illness, traits such as novelty seeking in mania or hypomania (14, 15). In a survey of 826 new patients presenting at a CAM clinic, 578 (70%) had a mental disorder and reported lower quality of life and greater levels of stress than those without a mental disorder. Among patients with a mental disorder, the major reasons for choosing complementary therapies were personal preference, interest, or beliefs in complementary therapies (44.3%) including as a treatment of last resort (30.7%) (16).

In a cross-sectional survey of 100 older (>55 years) inpatients and outpatients with bipolar disorder ($n = 50$) or major depression ($n = 50$), the use of herbal and nutritional compounds (HNC) was examined to determine several factors including, knowledge of products, perceived efficacy and safety, patterns of use and discussion of use with health care providers. Approximately 30% of respondents reported using oral HNC, 40% thought that they were Food and Drug Administration regulated and 14–20% preferred to take HNC to psychotropic medications (17).

A review of CAM therapies in the treatment of bipolar disorder, noted that few rigorous clinical studies have been conducted in this patient population (14). The herbal preparation Free and Easy Wanderer Plus has been examined as an adjunct to carbamazepine (CBZ) in a double-blinded, randomized placebo-controlled trial in patients with bipolar disorder in manic and depressive phases (18). When compared to CBZ monotherapy, at week 4 and 8 of the trial, the HM combined with CBZ resulted in significant improvement in depression but not mania.

Although cannabis has largely been seen as an illicit drug, it is now entering into conventional medicine under the rubric of "medicinal cannabis." Cannabis has been extensively researched in relation to its acute and chronic effects in psychosis. Discussion of the role of cannabis in bipolar disorder is beyond the scope of this article but is summarized in a systematic review and meta-analysis by Gibbs et al. (19). This reported that, on balance, in pre-existing bipolar disorder, cannabis may worsen the occurrence of manic symptoms and may also act as a causal risk factor in the incidence of manic symptoms.

This paper presents a systematic review of single and multiple-case reports of mania associated with herbal medicines other than cannabis. A more comprehensive understanding of what precipitates mania in vulnerable individuals may potentially lead to new understandings of the illness and the substrates that are implicated in bipolar disorders.

METHOD

This review of reports of herbal medicine-associated mania was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (20).

Inclusion Criteria: (a) published between 1980–2017 (b) in a peer-reviewed journal (c) included adult participants (> 18 years) (d) published in the English language. *Exclusion criteria:* (a) psychosis in the absence of manic features (b) secondary manias due to infection, neoplasm, epilepsy, and metabolic disturbances (c) systematic reviews (d) relating to cannabis.

Identification of Studies

In the first week of September 2017, a search of the electronic databases EMBASE, CINAHL, Health Source, PsychINFO and PubMed was conducted to find published associations between HM and mania. The search was commenced by identifying in each database the controlled vocabulary terms/ subject terms related to herbal medicines (group 1) and bipolar disorder (group 2). All subject terms were exploded. Subject terms in the respective databases for group 1 were herbal medicine (PubMed); herbal medicine and medicinal herbs and plants (EMBASE and PsychInfo); medicine and herbal medicine (CINAHL and Health Source). Additionally, 182 free text terms that related to herbal medicines, including botanical names, (see Appendix 1) were combined with "OR." Subject terms for group 2 were bipolar disorder, cyclothymic disorder (PubMed); bipolar disorder, cyclothymia (EMBASE and PsychInfo); and bipolar disorder (CINAHL and Health Source). The free text terms bipolar disorder, mania, cyclothymia, manic-depressive psychosis, manic state, bipolar depression and manic disorder were searched for and combined with "OR." Finally, group 1 and group 2 were combined with "AND."

A purpose-built coding sheet was used to assess articles against the inclusion criteria. To assess accuracy of initial screening KK and EB separately rated 20 titles and abstracts, randomly selected from the records screened using the RANDBETWEEN function in Microsoft Excel version 15.23.2. Inter-rater agreement on exclusion/inclusion was 100%.

Quality Assessment of Case Reports

Authors EB and KK individually assessed all included case reports for quality, according to the following nine criteria: classification on Quality Assessment Scale by Agbabiaka; use of a validated instrument to assess for causality (Naranjo or WHO-UMC score); botanical name of herbal medicine stated; herbal material assessed for authentication; herbal material assessed for adulteration; characteristics of herbal medicine detailed (e.g., plant part, extract type); product brand name and manufacturer detailed; batch numbers; herbal dosage specified. The case report Quality Assessment Scale by Agbabiaka (21) as modified by Hung, Hillier and Ernst (22) has 21 questions rated as "yes," "unclear," and "no," each item scored between 0 and 2 points for a total score out of 42 points. Each case report was classified as: low quality (0-14 points), lower medium quality (15–21 points), upper medium quality (22–28 points) or high quality (29–42 points) as recommended by Agbabiaka (21).

After each paper had been assessed EB and KK discussed the results and came to a consensus score. Inter-rater reliability on the Quality Assessment Scale by Agbabiaka was calculated using several indices: raw agreement (number of agreements for individual items divided by number of possible agreements), kappa coefficient and intraclass correlation coefficient (ICC). Raw agreement ranged from 52.4 to 95.2% for individual articles with mean raw agreement 75.6% (95% CI [71.2%, 80.1%]). Separate kappa coefficients were calculated between the two raters for all items on each of the 26 articles. To obtain mean kappa, the 26 kappa coefficients were first transformed using Fisher's transformation to achieve linearity. The mean and 95% CIs were calculated, then back-transformed to original kappa units. Individual kappa coefficients ranged from 0.16 to 0.92. Mean kappa was 0.60 (95% CI [0.50, 0.68]). Applying the criteria of Landis and Koch this represents a moderate-to-substantial level of agreement (23). The ICC between the two raters was calculated from the total score for each article using two-way ANOVA (24). Each item on the scale was rated as 0, 1, or 2. With 21 items the maximum possible score for an article was 42. Rater and article were treated as separate, random effects in the model. For total scores the means were 24.5 ($SD = 6.2$) for EB and 24.7 ($SD = 5.6$) for KK. The inter-article correlation between raters was 0.70 (95% CI [0.42, 0.85]). The ICC was 0.82 (95% CI [0.60, 0.92]) indicating a good-to-excellent level of agreement (25).

RESULTS

The results of the search strategy are summarized in the PRISMA diagram (**Figure 1**). There were no randomized clinical trials of HM in mania. The study sample comprised 35 case reports, from 19 single and 7 multiple-case reports, of an association between mania and use of HM. Details of each case report are summarized in Table S1, including clinical and demographic details, the composition of the HM, other medications, and treatment outcomes.

In summary, the reports included 17 females [age in years M(SD) = 43.1(13.2)] and 18 males [40.7(18.1)]. Case reports, grouped by HM (number of reports) comprised: St John's wort (*Hypericum perforatum*) (14); Ginseng (*Panax ginseng*) (5); brindleberry (*Garcinia cambogia*) (4); ma-huang (*Ephedra sinica*) (3); "herbal slimming pills" (2); Herbalife products (2); Hydroxycut (1); horny goat weed (*Epimedium grandiflorum*) (1); "herbal body tonic" (1); celery root (*Apium graveolans*) (1), and "herbal mixture" (1). Fourteen cases were taking concurrent prescription medications, comprising antidepressant (SSRI 3; SNRI 2; tricyclic 1; NDRI 1); lithium (1); antipsychotic (2); atypical antipsychotic (1); anti-epileptic (2); statin (2);

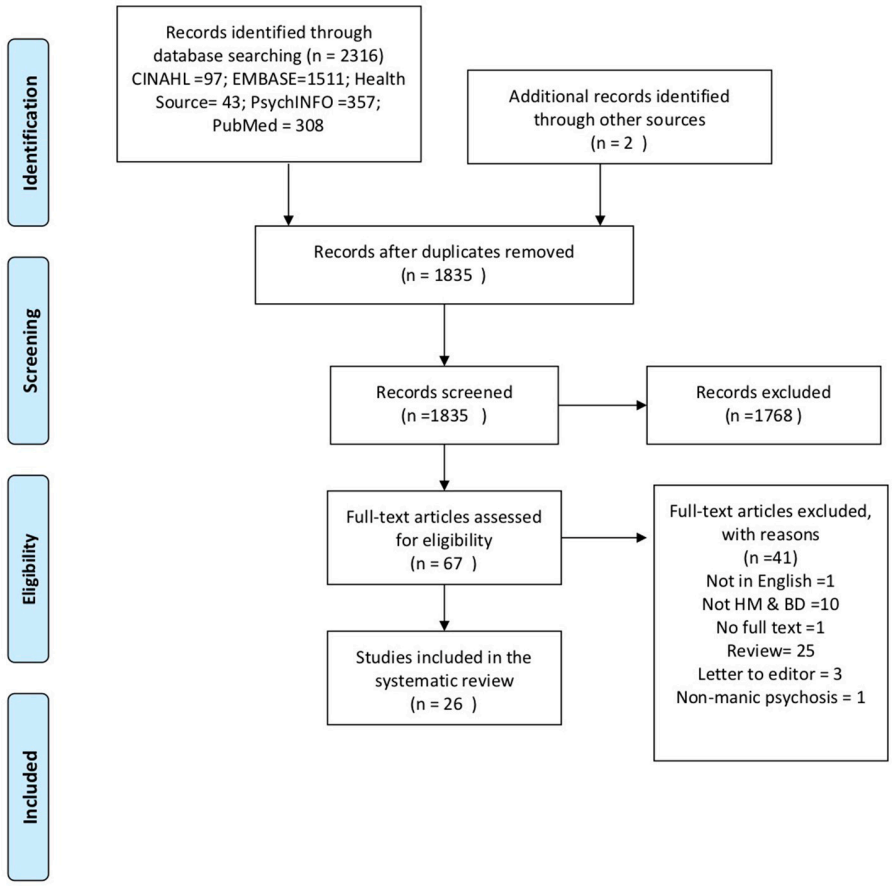

FIGURE 1 | Preferred reporting items for systematic reviews and meta-analysis flow diagram of included studies.

beta-blocker (1); NSAID (2); sildenafil (1) and a synthetic glucocorticoid (1). A psychiatric history was noted in 24 of the 35 cases of HM-associated mania, diagnoses included depression ($n = 11$) bipolar disorder type I (BDI) ($n = 5$), bipolar disorder type II (BDII) ($n = 2$), post-traumatic symptoms ($n = 1$), eating disorder ($n = 2$), past suicide attempt ($n = 1$) and substance/medication-induced bipolar and related disorder ($n = 1$). For the whole sample the time to onset of manic symptoms from commencing the HM was between 2 days and 2 years with a median of 4 weeks.

St John's Wort (*Hypericum perforatum*)

Fourteen case reports described mania, hypomania and two mixed states associated with St John's wort, in seven females [age in years M(SD)=49.4(12.4)] and seven males [39.4 (17.8)]. Stated reasons for taking St John's wort were depression (12) (26–34), to improve energy (1) (29) and to relieve symptoms of post-traumatic stress (1) (29). The time of onset of manic symptoms from commencing HM ranged from 3 days to 2 months. The mental status on examination was consistent with mania and two mixed state in the 14 cases. Three cases had a past psychiatric history of bipolar disorder, and eight of unipolar depression of whom four were concurrently taking antidepressants. In eight cases, the dose of the St John's wort preparation was not specified.

Ginseng (*Panax ginseng*)

There were five case reports of *Ginseng*-associated mania in our study sample, two females [46(10) years] and three males [42.7(25.7)]. Stated reasons for taking *Ginseng* were to boost energy (2) (35, 36), fatigue (1) (37), erectile dysfunction (1) (34) and one unknown (1) (38). The time to onset of symptoms between taking *Ginseng* and mania ranged between 10 days and 2 months prior. Of these five cases, two had a prior history of depression, one of substance-induced hypomania, two had no past psychiatric history. The reported range of daily doses of *Ginseng* in the case reports were 500–750 mg of root or 300mg—20 g of extract, compared to a recommended short-term dose range of 0.5–2 g of dry *Ginseng* root, equivalent to 200–600 mg of extract, and long-term dose of 1 g of dry root (39). In two cases, the recommended long-term dose was far exceeded.

Brindleberry (*Garcinia cambogia*)

There were two case reports of mania and one each of manic psychosis and hypomania, involving *Garcinia cambogia*,

2 females [42.5(8.5) years] and 2 males [37.5(12.5)]. The stated reason for taking the HM was weight loss (40, 41) and three patients had a past history of bipolar disorder. In each case, the dose of *Garcinia cambogia* was not specified. The time to onset of manic symptoms from commencing the HM ranged from 2–6 weeks. Two cases were concurrently taking antidepressants and mood stabilizers.

Ma-Huang (*Ephedra sinica*)

In three cases, ma-huang (in one case along with chromium picolinate and caffeine) was associated with manic-like symptoms in individuals without a history of bipolar illness, two females [30.5(9.5) years] and one male [45 years]. Stated reasons for taking the HM were weight loss (42, 43) and heightened alertness and to prevent drowsiness (44). Past psychiatric history included hospitalization for alcohol poisoning, and bulimia without purging with a description of manic-like symptoms. The family psychiatric history included possible bipolar disorder and schizophrenia. The time to onset of manic symptoms ranged between 5 days and 2 months. In each case the dose of the HM was unknown, concurrent medication in one case comprised thyroid hormone and recently discontinued antidepressant.

Herbalife Products

Two cases reported mania associated with the use of a Herbalife product for the stated reason of weight loss (45, 46). Both were male [32.5 (6.5)] and neither had a personal or family history of bipolar disorder or were taking prescribed medication. In one case, the patient became manic after taking "large amounts" of the products both as tablets and tea. The time to onset of manic symptoms ranged between 2 and 20 days. In a subsequent published letter regarding the above case reports, by authors affiliated with the Herbalife brand, (47), it was noted that the case reports did not specify the precise product (as opposed to the brand) and/or ingredients taken in these two cases.

Herbal Slimming Pills

In a multiple-case report by Chong, two cases of manic-like psychosis were associated with the use of "Herbal slimming pills" (48). An assay of the HM identified that it contained the anti-depressant pharmaceutical sibutramine. The authors attributed the occurrence of mania to this adulterant.

There were five single case reports that related an HM (ingredients see Table S1) to mania, involving Hydroxycut (49), Horny goat weed (*Epimedium grandiflorum*) (50), "herbal body tonic," prescribed for anger (51), celery root (*Apium graveolans*) for menopausal symptoms (52) and a "herbal mixture" prescribed for fatigue (53).

QUALITY ASSESSMENT OF CASE REPORTS

In addition to the systematic review of HM associated mania, we also assessed the quality of the individual case reports. The results are shown in Table S2.

Applying Hung, Hillier and Ernst's (22) modified version of the Agbabiaka tool (54), the distribution of the quality assessment scores across the 26 papers, covering 35 case reports, was as follows: low quality (0), lower-medium quality (9), upper-medium quality (10) and high quality (7). Only one single case report used a validated instrument to assess causality, the Naranjo scale. The botanical name was listed in 19 cases in 18 papers. Only 1 paper presenting 2 case reports used a laboratory assay to confirm the composition of the HM. The composition of the HM, for example plant part used and extract type, was detailed in only 1 case report. The brand name and manufacturer were stated in 3 case reports. The dosage of the HM was specified in only 18 of the case reports. Of the study sample, 2 case reports of 1 HM were assessed for adulteration. The batch number was provided in none of the case reports. Herbal dosage was detailed fully in 6 and partially in 3 cases.

DISCUSSION

This review examined case report evidence regarding HM-associated mania. Those included were: St John's wort (*Hypericum perforatum)*; Ginseng (*Panax Ginseng)*; Brindleberry (*Garcinia cambogia)*; ma-huang (*Ephedra sinica*); "herbal slimming pills"; Herbalife products; Hydroxycut; horny goat weed (*Epimedium grandiflorum*); "herbal body tonic"; celery root (*Apium graveolans*), and "herbal mixture." Where possible the candidate pathophysiological mechanisms are discussed in turn, as are other factors which may have contributed to the onset of mania in the individuals included in the study. There is an inherent difficulty in making attributions regarding the causality of HM on mania as the course of bipolar disorder is unpredictable.

Of the 35 case reports included in this review, 5 were isolated reports of one HM and two cases (both "herbal slimming pills") were attributed to a contaminant. The remaining 28 cases were accounted for by five HM, all of which were the subject of two or more case reports of mania. Over a publication period of 38 years (1980–2017) this is a small yield of reported concurrence of HM usage and mania. The small numbers and unreliability of discerning and reporting a link between mania and HM preclude any definitive statement as to whether any association is causal or coincidental.

With respect to St John's wort, there is a high specificity of the stated reason for taking the HM to be for treatment of depression (11 of 14 St John's wort cases compared to 0 of 21 other HM). There was also greater morbidity in the psychiatric history of the St John's wort cases (13 of 14 cases compared to 11 of 21 for other HM), in the family history of mood disorder (6 of 14 compared to 2 of 21) and concurrent antidepressant prescribing was more common (4 of 14 compared to 4 of 21). Competing explanations for these patterns include an increased diathesis toward bipolar disorder, fluctuations of established affective illness, antidepressant-associated mania and HM-associated mania. These factors are not mutually exclusive, for instance according to Craddock and Sklar, a family history of bipolar disorder is an important clinical predictor of a likely bipolar course in a patient who presents with one or more

episodes of depression even before their first personal episode of mood elevation (55).

The mechanism by which St John's wort may alter susceptibility to mania is not well understood. As with antidepressants, it is difficult to distinguish spontaneous episodes of mania from St John's wort-associated switching (56). Angst et al. analyzed the time course and risk factors for a diagnostic change from major depression to bipolar disorders over an average of 20 years from onset. Diagnostic change from depression to bipolar type I occurred in approximately 1% and bipolar type II 0.5% of patients per year (57). In patients with major depressive disorder treated with antidepressants, it has been found that antidepressant-associated mania or hypomania occurs at an average frequency of 3.42% of cases per year, but it is unclear to what extent switching represents undiagnosed bipolar disorder or a direct pharmacological effect of antidepressants (58).

Depression is one of the most commonly cited reasons for using CAM (59). The prevalence of depression in the United States has been reported to have increased between 2005 and 2015 (60). For many patients with depression, HM which are in many countries, predominantly available over-the-counter, may be an attractive alternative to conventional medicines. There is a substantial evidence base from randomized controlled trials supporting the use of St John's wort in mild-to-moderate depression. In a systematic review and meta-analysis comprising 23 randomized trials of St John's wort in outpatients with mild-to-moderate depression ($N = 1757$), it was found that *Hypericum perforatum* extracts were significantly more effective than placebo (61).

St John's wort has a variety of actions that may contribute to its therapeutic effects. *In vitro*, it acts on neurotransmitter regulation, including beta adrenergic and glutamate receptors, and ion channel conductance. Hypericin (an active constituent of St John's wort) inhibits serotonin reuptake, and 5-HT_{1A} and 5-HT_{1B} receptor changes are associated with prolonged use (62). According to Fahmi et al, in animals, hypericum is effective in three major biochemical systems relevant for antidepressant activity including inhibition of synaptic reuptake of serotonin, noradrenaline and dopamine (26). In the human case reported by Barbenel of concurrent prescribing of St John's wort and sertraline in a patient following surgery for crypto-orchidism, alteration of testosterone and gonadotrophin levels and interactions of antidepressant and St John's wort were further considerations.

With five case reports of *Ginseng* associated mania it was the second most commonly reported HM after St John's wort. Based on the belief that it is a panacea and promotes longevity, *Ginseng* root has been used for over 2000 years (63). There are a number of plants that share the common name *Ginseng* however only three of these are from the genus Panax (*Panax ginseng, P. notoginseng* and *P. quinquefolius*). Other "ginsengs" include Siberian (*Eleutherococcus senticosus*), Indian (*Withania somnifera*), and Brazilian (*Pfaffia paniculata*) (64, 65). The most important constituents of Panax ginseng are the ginsenosides, of which 15 different types have been identified (35).

In a systematic review of RCTs examining the efficacy of *Panax ginseng* root extracts for a number of indications, it was concluded that there is contradictory evidence that *Ginseng* improves physical performance and immunological measures. It may have beneficial effects on psychomotor performance and cognitive behavior. No trial has confirmed the alleged age-delaying properties of *Ginseng*. Results suggesting a reduction of blood glucose levels in type-II diabetic patients require further investigation (64, 65). With *Panax ginseng*, two mechanisms of action in depression have been advocated, firstly, an activating effect of ginsenosides on the HPA-axis resulting in elevated corticotropin and corticosteroid levels (33). Secondly, monoamine signaling could also be affected by ginsenosides (66, 67).

Thirteen of 35 case reports in our study sample involved adverse psychiatric effects of weight loss products including brindleberry (*Garcinia cambogia*), ma-huang (*Ephedra sinica*), "herbal slimming pills," Herbalife products and Hydroxycut. The social stigma of obesity, a desire to lose weight without making drastic lifestyle changes, and frustration at previous failed attempts are commonly reported reasons for using dietary supplements which are readily available and advertised as being "natural" and safe (68).

In one 12-week randomized placebo-controlled trial, *Garcinia cambogia* failed to produce significant weight loss and fat loss beyond that observed with a placebo (69). In contrast, another double-blind placebo RCT found that *Garcinia cambogia* reduced abdominal fat accumulation in participants (70). Other human research has confirmed the potential of *Garcinia cambogia*/HCA in stimulating fat oxidation, increasing serotonin release in brain cortex and normalizing lipid profiles (71). The main active ingredient of *Garcinia cambogia* is hydrocitric acid which has serotonergic effects and has been implicated in serotonin syndrome (38). Hydrocitric acid is the putative mediator of this HM weight loss effect; it is thought to promote the release and synaptic availability of serotonin thus influencing appetite (41). The effects of Hydroxycut were attributed to the inclusion of *Garcinia cambogia* in the preparation (49).

Partin and Pushkin, who reported a case of hypomania associated with horny goat weed (*Epimedium grandiflorum*) proposed that this may have been due to the addition of other unidentified herbs and pharmaceuticals (50). However, these were not explicitly tested for.

Ma-huang (*Ephedra sinica*) is native to China and Mongolia and contains sympathomimetic compounds known as *Ephedra* alkaloids. Traditionally used to treat asthma and hay fever symptoms, more recently it has been combined with caffeine or botanical sources of caffeine (for example *Guarana*) for weight loss purposes (68). In a 6–month RCT of herbal *Ephedra*/caffeine for weight loss, it was found that 90/192 mg/day of herbal *ephedra*/caffeine promoted weight and body fat reduction (72). In another randomized double-blind trial of a herbal supplement containing ma-huang-guarana for weight loss, it was found that the active treatment produced significant effects (73). Ma-huang contains variable amounts of ephedrine congeners which enhance norepinephrine release in central noradrenergic

neurons. Ephedrine also has direct agonist activity at alpha and beta-adrenergic receptors (44).

Sibutramine is an appetite-suppressing agent that is a norepinephrine and serotonin reuptake inhibitor, initially developed as an antidepressant (48) its use has been associated with mania (74, 75) and hypomania (76). In a recent analytical study of 447 weight loss products, 119 were found to be adulterated with one or more weight loss compounds including sibutramine, its metabolites benzyl sibutramine and desmethyl sibutramine; phenolphthalein; bisacodyl; furosemide; liothyronine (T3); and thyroxine (T4) (77). This demonstrates the importance of having regulatory bodies oversee CAM manufacturing practices and to regularly assess certain classes of CAM products for adulterants (such as weight loss products). These incidences of mania associated with HM weight-loss products highlight the fact that they may be considered safe and harmless by consumers when they have the propensity to trigger adverse events in vulnerable individuals (78).

Khalid et al. reported a case of mania associated with celery root (*Apium graveolans*), St John's wort (*Hypericum Perforatum)* and venlafaxine. Mania ensued shortly after the ingestion of celery root, which belongs to a group of plants classified as the umbelliferous family, which contain phytoestrogens that are structurally similar to estrogen. In this case the patient developed elevated serum venlafaxine levels after taking celery root for menopausal symptoms, suggesting pharmacokinetic potentiation of the venlafaxine level by the celery root as a likely mechanism of induction of mania (52).

Thirteen of the patients were concurrently taking conventional medicines (as shown in Table S1) as well as HM which may have led to herb-drug interactions resulting in mania. This might result from alterations of absorption, distribution, metabolism or elimination of a conventional drug by a herbal product, that is pharmacokinetic effects (79). Alternatively, there may be synergistic effects of a HM and a conventional medicine reflecting common mechanisms of action such as neurotransmitter regulation. Drug dosage is one important factor in such herb-drug interactions as well as in interactions with underlying biological diatheses (80). In approximately one third of the cases reviewed the dosage of the HM was unknown. This limits the ability to make causal inferences regarding the dose of the HM associated with a manic switch in vulnerable individuals.

For the whole sample the time to onset of manic symptoms from commencing the HM (treatment-emergence interval) ranged between 2 days and 2 years with a median of 4 weeks. None of the HM reported associated with mania diverged notably from this median time to onset of manic symptoms. A treatment-emergence interval of 8–12 weeks is deemed to implicate causality; however, a much shorter interval may be necessary to definitively link cause and effect (81). The manic episodes reported in the cases were mostly treated with conventional anti-manic agents, only two reports indicate the outcome of cessation of the HM alone on the course of mania, one indicating remission in 2 days, the other no improvement following a switch into depression. Thus, no general statement can be made with respect to mania resolution on ceasing the implicated HM.

In addition to the systematic review of HM-associated mania, we also assessed the quality of reporting (Table S2) on the modified Quality Assessment Scale by Agbabiaka, in each of the 26 published case report papers. The case report quality assessment score ratings were low quality (0), lower-medium quality (9), upper-medium quality (10) and high quality (7). There are two algorithm-based rating instruments to assign the probability that an adverse event (in this case mania or hypomania) is related to a given exogenous substance, the Naranjo and the WHO-UMC. Of the cases reviewed only one used the Naranjo scale, none used the WHO-UMC. One study compared the two rating scales and found that the WHO-UMC method was more simple and less time consuming compared to the Naranjo probability scale (82). On the 7 additional quality criteria, the quality of reporting was satisfactory only for the inclusion of botanical name of HM (26 of 35 cases) and to a lesser extent HM dosage (18 of 35 cases). On the remaining 5 criteria less than 10% of papers were compliant. It is noted that many of the reports were published before the advent of defined quality criteria ratings, for example 19 of the 26 papers preceded the publication of the modified Quality Assessment Scale by Agbabiaka in 2008. Future published case reports of adverse events should adhere to such criteria in order to improve their overall quality and inferences which may be made from these articles.

The current review of case reports is subject to a number of limitations. Substance/medication-induced bipolar and related disorder may reflect a switch in a previously unexpressed bipolar diathesis. It is possible that the reports in the scientific literature are subject to a confirmation bias in that clinicians are looking for links between mania and recent use of HM. There is also a possible effect of researcher/ publication bias, which has led to the publication of the included studies. Ethically, it is difficult to replicate studies which suggest a potentially harmful effect of various HM.

The compilation of case histories presents a different sample to that commonly seen in a randomized controlled trial setting where fixed inclusion and exclusion criteria apply. This sample of putative HM induced mania includes a number of patients ($n = 7$) with a stated past history of a diagnosis of BD and a further 7 patients without a BD diagnosis taking antidepressants. This increases the likelihood that the observed manic episode was attributable to extant bipolar disorder or antidepressant induced switching rather than the HM *per se*, although interactions of these variables cannot be excluded.

Despite these limitations, however, there are a number of strengths associated with the inclusion of case reports including that the patients, episodes of mania, time course of symptoms and aetiological factors are described in detail, as reflected in Table S1. The authors are generally circumspect in their judgements regarding causality, documenting an observed association, summarizing knowledge regarding possible mechanisms of action, and allowing for the multiplicity of explanations that attend a disorder of unclear etiology and pathogenesis and with a typically fluctuating course.

Concepts of exogenous and endogenous causation of psychoses have been debated over the past century. In 1910,

Bonhoeffer proposed that the brain only manifested a few stereotyped mental reactions, whether from exogenous or endogenous origins. He recognized delirium in particular as a presentation that could follow diverse exogenous causes. The typical features in delerium of clouding of consciousness and disorientation form the rationale for categorizing it separately to the psychoses (83). Similarly, in the concept of unitary psychosis, as elaborated by Conrad in 1959, there is no fixed relationship between symptom picture and exogenous factors, the latter potentially triggering a range of symptom pictures (84). Relating these propositions to the current study on case reports of mania associated with herbal medicines, the results are inconclusive because it is restricted to one diagnostic category, mania, and one class of aetiological factors, herbal medicines. Comparisons of reports of herbal medicines associated with the onset of a variety of mental disorders would yield information as to whether the relationship indicates specific aetiologies of a disease (e.g., mania) or a broader relationship whereby a diversity of diagnostic categories (e.g., mania, psychotic depression and schizophrenia) are attributable to a common aetiological factor, the unitarian view.

In summary, the reported co-occurrence of HM usage and mania, whilst inconclusive, provides a plausible signal as to brain mechanisms relevant to the pathogenesis of mania. With the increasing storage of health information in electronic health records and evolving techniques of data mining there are prospects for the widespread application of case report level information to the elucidation of associations and causal links between usage of HM and the occurrence and varied course of mental disorders including BD.

AUTHOR CONTRIBUTIONS

EB developed the concept of the article from which she received supervision and expert advice in the area of psychiatry from KK, statistics from MG, neurology from BT and complementary medicines from JH.

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SUPPLEMENTARY MATERIAL

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Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

APPENDIX

	Search terms
1	Achillea
2	Adaptogen
3	Albizia
4	Anemone
5	Angelica
6	Asafoetida
7	Ashwagandha
8	Astragalus
9	Atropa
10	Avena
11	Bacopa
12	Ballota
13	Banxia-houpo-tang
14	Betony
15	Bitter orange
16	Borage
17	Borago
18	Botanicals
19	Californian poppy
20	Camellia
21	Cannabis
22	Catmint
23	Catnip
24	Centella
25	Chamomile
26	Chinese medicine
27	Citrus
28	Clove
29	Codonopsis
30	Cola
31	Convallaria
32	Corni fructus
33	Cornus officinalis
34	Corydalis
35	Cowslip
36	Cramp bark
37	Crocetin
38	Crocin
39	Crocus
40	Crocus sativus L.
41	Cyclothymia
42	Cypripedium
43	Damiana
44	Datura
45	Deadly nightshade
46	Dioscorea
47	Dong quai
48	Echium amoenum
49	Eleutherococcus
50	Ephedra sinica
51	Ephedrae herba
52	Eschscholzia
53	Ferula
54	Ganoderma
55	Gelsemium
56	Ginseng
57	Glycyrrhiza
58	Goldenrod
59	Gotu kola
60	Gou qi zi
61	Green tea
62	Guarana
63	Hange-koboku-to
64	Happiness bark
65	Henbane
66	Herbal medicine
67	Herbs
68	Hoelen
69	Hops
70	Humulus
71	Hyoscyamus
72	Hypericum
73	Indian snakeroot
74	Jamaican dogwood
75	Jimson weed
76	Kampo
77	Kampo Medicine
78	Kanpo
79	Kanpo Medicine
80	Kava
81	Kava-Kava
82	Kola nut
83	korean ginseng
84	Koso-San
85	Lactuca
86	Lady's slipper
87	Lavandula
88	Lavender
89	Lemon balm
90	Leonurus
91	Licorice
92	Lily
93	Linden
94	Lobelia
95	Lotus
96	Lycii Fructus
97	Lycium barbarum
98	Ma-Huang
99	Magnolia
100	Marrubium
101	Matricaria
102	Melissa
103	Mentha
104	Mistletoe
105	Mitchella
106	Motherwort
107	Mystica
108	Nelumbo
109	Nepeta
110	Nervine
111	Nutmeg
112	Nux vomica
113	Oat
114	Ocimum
115	Opium poppy
116	Panax
117	Papaver
118	Passiflora
119	Passion flower
120	Paullinia
121	Peppermint
122	Phytomedicine
123	Phytotherapy
124	Pinellia ternate
125	Pinelliae rhizome
126	Piper
127	Piper methysticum
128	Piscidia

	Search terms
129	*Plant extract*
130	*Plant preparation*
131	*Poria*
132	*Primula*
133	*Prunus*
134	*Pulsatilla*
135	*Rauvolfia*
136	*Rauwolfia*
137	*Rehmannia*
138	*Reishi*
139	*Rhodiola*
140	*Rhodiola rosea*
141	*Rosemary*
142	*Rosmarinus*
143	*Rosmarinus*
144	*Saffron*
145	*Safranal*
146	*Saffron extract*
147	*Saint John's wort*
148	*Sceletium*
149	*Schisandra*
150	*Scutellaria*
151	*Shan zhu*
152	*Sheng ban xia*
153	*Siberian ginseng*
154	*skullcap*
155	*Solidago*
156	*Stachys*
157	*St John's Wort*
158	*Sutherlandia*
159	*Syzygium*
160	*Thornapple*
161	*Thymoleptic*
162	*Tilia*
163	*Traditional Chinese medicine*
164	*Tulsi*
165	*Turnera*
166	*Valerian*
167	*Valeriana*
168	*Verbena*
169	*Vervain*
170	*Viburnum*
171	*Viscum*
172	*White horehound*
173	*Withania*
174	*Wild cherry*
175	*Wild lettuce*
176	*Wild yam*
177	*Xiang Su San*
178	*Yan hu suo*
179	*Yarrow*
180	*Yellow jasmine*
181	*Zizyphus*
182	*Free AND Easy Wanderer Plus*

1. Bipolar depression
2. Bipolar disorder
3. Bipolar Disorder
4. Mania
5. Manic disorder
6. Manic state

Table 1. Details of each case report

Author (date)	Gender (age years)	Name of preparation	Dose of preparation	Reason for taking HM	Time to onset of manic symptoms	Concurrent medications	Mental State at presentation	Diagnosis	Hospitalized	Psychiatric history	Family psychiatric history	Medical history	Treatment outcomes
Barbenel et al. (2000)	M (28)	St John's wort	Unknown	Depression	5-8 weeks	Sertraline 50mg daily	over-aroused, distractible, flight of ideas, grandiose delusions	Manic episode	Yes	Referred for assessment of symptoms of depression	Depression in 5 brothers	Concomitant testosterone since bilateral orchidectomy. Wolff-Parkinson-White	Unknown
Dalwood et al. (2015)	M (39)	St John's Wort	"twice recommended dosage"	Low mood	4 weeks	None	Manic symptoms not elaborated	Manic episode	Yes	None	None	Unknown	Mania resolved after cessation of St John's wort and commencement of mood stabilizer medications
Fahmi et al. (2002)	F (28)	Hypericum	Average 18g/day	Depressive symptoms	2 weeks	None	Hyperactive, disorganized, pressured speech. Mood elevated, irritable. Flight of ideas, paranoid delusions.	Acute mania	Yes	18-month history of depression	None	None	Olanzapine and sodium valproate (doses unknown). Manic symptoms gradually resolved over three to four weeks
Moses & Mallnger (2000)	F (70)	St John's wort	3 x 300 then 2 x300 mg/day	Depression	2 weeks	Notriptyline 75mg, bupropion 75mg daily	Insomnia, early waking, reckless spending, increased activity, careless	Not listed	Unclear	8 year history of recurrent depression	None	Ménière's disease, left internal capsule infarct	After two weeks she reported sleeping 8hrs per night, good spirits, less careless, not over-spending. Decreased St John's wort to one tablet, added valproic acid 750mg per day
Moses & Mallnger (2000)	M (53)	St John's wort	900 mg/day	Depression	Shortly after	Unknown	increased self-esteem, racing thoughts, talkative, sleep decreased, libido increased, reckless spending, driving faster, visual hallucinations.	Current diagnosis not listed	Unclear	Behaviors consistent with bipolar type II	Son bipolar type I, daughter depression	None	Discontinued St John's wort initiated lithium 900mg per day
Moses & Mallnger (2000)	F (61)	St John's wort	Unknown	Improve energy	2 weeks	Olanzepine 20mg daily, lithium	Flamboyantly dressed, referential delusions, paranoia, erotomanic	Psychotic Mania	Yes	Bipolar type I disorder	Unknown	hysterectomy, benign pulmonary nodules, thyromegaly	Re-admission after 3 days for suspected medication-related delirium
Nierenberg, Burt et al. (1999)	M (20)	St John's wort	0.2 % hypericum, 300 mg tds	Major depression	3 days	None	Extreme agitation, irritability, pressured speech, pacing, anxiety	Not listed	Yes	Depression	Uncle bipolar disorder	None	Discontinued St John's wort. Lithium 450mg twice day, clonazepam
Nierenberg, Burt et al. (1999)	F (51)	St John's wort	300 mg tds	Stressed and depressed	A few days	None	Speech disorganized, giggling uncontrollably, hypermotoric, hypersexual.	Not listed	Yes	Psychotic mania	Unknown	None	Lithium 600mg bd
O'Breasail & Aigouarch (1998)	M (76)	St John's wort	Unknown	Depression	6 weeks	Venlafaxine 37.5 mg tds	Increased drive, overactive, pressured speech, irritability, euphoric grandiose plans. Reduced sleep and concentration	Hypomania	Yes	Depression	Depression & suicide	Cerebral vascular accident affecting right side. Atrial flutter	Valproate
O'Breasail & Aigouarch (1998)	M (28)	St John's wort	Unknown	Posttraumatic stress symptoms	Approximately 3 months	None	Flight of ideas, pressured speech, agitated, irritable, grandiose delusions	Bipolar disorder, acute manic episode	Yes	Posttraumatic stress symptoms	Mother depression	Shoulder injury	Mood stabilization with lithium carbonate
Raja & Azzoni (2006)	F (47)	Hypericum, Ilex paraguayensis, cannabis.	Undetermined dosage	Major depression	6 months	Previously paroxetine 20mg daily	Mixed state, unstable mood, crying, dysphoric, irritable, logorrhea, motor hyperactivity, distractability, agitation, excessive sexual arousal, insomnia	Mixed state	Unclear	Major depression	Not listed	Not listed	Oxcarbazepine (up to 1200mg), clonazepam (up to 4mg) per day
Raja & Azzoni (2006)	M (32)	Hypericum	Dosage unknown	Depression	4 weeks	None	Sad, anxious, guilt, nervous, irritable, inconsistently hyperactive with racing thoughts, logorrhea, distractable, decreased sleep	Bipolar disorder, mixed state	Yes	Depression	Cousin schizoaffective, bipolar type	Not listed	Full remission after 11 days, discharged on valproate
Schneck (1998)	F (47)	St John's wort	0.1% tincture	Depression	10 days	Previously sertraline 50 mg daily	Racing and distorted thoughts, increased irritability, hostility, aggressive behavior, decreased sleep.	Hypomania	Unclear	Panic disorder and major depressive episode	Unknown	Not listed	Discontinued St John's wort, complete resolution of symptoms in 2 days
Spinella & Eaton (2002)	F (42)	Ginkgo biloba, melatonin, St John's wort	Unspecified doses	Depression	Past several weeks	Fluoxetine, buspirone	Disrupted sleep-wake cycle, insomnia, racing thoughts, agitation, pressured speech.	Hypomania	Unclear	Depression and anxiety	Unknown	Cervical sprain, concussion	Advised to cease all non-prescription medication, remained depressed
Engelberg et al. (2001)	M (26)	Chinese red ginseng root	250mg 2-3 caps per day	Boost energy	2 months	None	Pressured speech, racing thoughts, grandiosity, irritability. Thought form circumstantial, tangential, loose associations, poor insight.	Manic symptoms	Yes	None	None	None	Ceased the supplement 14 hours prior to admission. Valproic acid 500mg bd, Lorazepam 1mg daily. Euthymic after 10 days
Gonzalez-Seijo et al.(1995)	F (35)	Panax ginseng	"1 tablet" daily	Unknown	10 days	Previously lithium carbonate 1200mg, amitriptyline 75 mg daily	Euphoric, hyperactive, talkative, singing, spending and affective lability, irritable and aggressive. Little sleep	Manic episode	Yes	Depression with hospitalization	Unknown	None	Haloperidol 7.5mg, lithium carbonate 1000 mg per day. Symptoms resolved in 48 hours
Norelli & Xu (2014)	M (23)	Asian red ginseng	Estimated 15g ginseng daily	Boost energy	1 month	None	Increased psychomotor activity, pacing, pressured speech, racing disorganized thoughts, anxious, irritable, labile affect, auditory hallucinations	Acute manic psychosis	Yes	None	None	None	Risperidone 1mg daily. Symptoms remitted after 3 days
Norelli & Xu (2014)	M (79)	Korean ginseng, yohimbine	Estimated 20g ginseng daily	Erectile dysfunction	2 months	Unknown	Motor restlessness, pressured speech, anxious mood, labile affect, racing disorganized thoughts, paranoid ideas	Acute manic psychosis	Unclear	Substance-induced hypomanic episode associated with yohimbine	Unknown	Mild hypertension	"a short course of antipsychotic treatment"

Table 2. The quality of individual case reports

Publication	Case Report Quality Assessment Score	Validated instrument to assess causality	Botanical name of HM	Herbal Material assayed for authentication	HM composition detailed*	Brand name and manufacturer stated	HM dosage specified
Barbenel et al 2000	26 upper medium	No	Yes	No	No	No	No
Dalwood et al 2015	23 upper medium	No	Yes	No	No	No	No
Fahmi et al 2002	29 high	No	Yes	No	No	No	Yes
Moses & Mallinger 2000	30 high	No	Yes	No	No	No	Yes, Yes, No
Nierenberg et al 1999	34 high	No	Yes	No	No	No	Yes, Yes
O'Breasail & Argouarch 1998	19 lower medium	No	No	No	No	No	No, No
Raja & Azzoni 2004	21 lower medium	No	Yes	No	No	No	No, No
Schneck 1998	26 upper medium	No	Yes	No	No	No	Yes
Spinella & Eaton 2002	27 upper medium	No	Yes	No	No	No	No
Engelberg et al 2001	33 high	No	Yes	No	No	No	Yes
Gonzalez-Seijo et al 1995	21 lower medium	No	Yes	No	No	No	No
Norelli & Xu 2015	27 upper medium	No	Yes	No	No	No	Yes, Yes
Vazquez & Aguera-Ortiz 2012	27 upper medium	No	Yes	No	Yes	No	Yes
Cotovio & Oliveira-Maia 2017	23 upper medium	No	Yes	No	No	No	No
Hendrickson et al 2016	18 lower medium	No	Yes	No	No	No	Yes, Yes, Yes
Boerth & Caley 2003	21 low medium	Yes	Yes	No	No	No	No
Capwell 1995	30 high	No	Yes	No	No	No	No
Emmanuel et al 1998	18 lower medium	No	No	No	No	No	No
Guzel Ozdemir et al 2015	15 lower medium	No	No	No	No	Yes	Yes
Katz 2000	30 high	No	No	No	No	Yes	Yes
Chong 2000	26 upper medium	No	No	Yes	No	No	No, No
Partin & Pushkin 2004	23 upper medium	No	Yes	No	No	No	Yes
Narasimha et al 2013	28 upper medium	No	No	No	No	Yes	Yes
Saatcioglu et al 2007	16 lower medium	No	No	No	Yes	No	No
Kelly et al 2001	22 upper medium	No	No	No	No	No	No
Khalid et al 2016	31 high	No	Yes	No	Yes	No	Yes

*Note: *detailed both plant part used and extract type*

Chapter 6

General Discussion

This thesis has examined a number of perspectives on causation and pathogenesis of mania in bipolar disorder (BD) in particular through a series of comparisons with a reference condition, temporal lobe epilepsy (TLE). These studies have concluded that BD and TLE share some common features with respect to precipitants of mania and seizures (chapter 2), and cognitive impairments in euthymic BD and pre-surgical TLE (chapter 3). The possible application of an evidence-based treatment for refractory epilepsy, the ketogenic diet, as a treatment for mental disorders has been examined (chapter 4). Finally, evidence that herbal medicine may precipitate manic episodes is summarised (chapter 5).

The first section of this final chapter summarises the main results from the individual studies in chapters 2-5, with a particular focus on findings that shed some light on the pathophysiological mechanisms and neural substrates involved in the occurrence of manic episodes. The second section discusses limitations of these studies. The third section addresses directions for future research arising from the findings which may lead to development of improved treatments for individuals with bipolar disorder.

[*Note:* temporal lobe epilepsy (TLE) is also referred to as partial seizures (PS) and focal seizures (FS) arising from the temporal lobe reflecting changing nomenclature over time as discussed on page 23 of the thesis]

6.1 Summary of results

6.1.1 Precipitating factors for mania and partial seizures

Chapter 2 reviewed precipitating factors in humans for both mania and partial seizures (PS). The precipitants common to both disorders included stress, sleep deprivation, antidepressant medication and more tentatively emotion. Precipitating factors for mania alone included goal-attainment events, spring and summer seasons, postpartum, and

drugs including steroids and stimulants. For PS alone precipitating factors included winter season, menstruation, and specific triggers in complex reflex epilepsy.

The precipitants common to both - stress, sleep deprivation and antidepressant medications - are suggestive of shared pathophysiology between the two disorders.

The mechanisms by which stress can alter the susceptibility for mania or PS are not well understood but are thought to include both neurological (HPA axis dysfunction) (Phillips 2007) endocrinological pathways (adrenocorticotropic hormone and cortisol) (Joëls 2009) and the interaction between the two, as detailed in chapter 2. Stress is rarely experienced in isolation and is often present with other precipitating factors, for example sleep deprivation.

The effect of sleep deprivation/reduction is thought to be a final common pathway in the onset of mania whereby insomnia is also a feature of mania and may exacerbate mania, a self-reinforcing cycle, with or without initiation by other precipitants (e.g., stress) (Wehr, Sack et al. 1987). Changes in sleep patterns may act as a marker for manic or depressive episodes. In healthy individuals, sleep deprivation may elicit paroxysmal EEG activity (Rodin, Luby et al. 1962). In epilepsy a reduction of even 1.5 hours of sleep is correlated with an increase of seizures (Rajna and Veres 1993). It is interesting to note that sleep deprivation has been used as a treatment for both bipolar and unipolar depression for many years (Svendsen 1976). The hypothesised mode of action of antidepressant effects of sleep-deprivation therapy is thought to be related to the clock genes and circadian rhythms. Sleep-deprivation therapy is thought to reset abnormal clock gene machinery. Relapse of depressive symptoms during recovery-night sleep reactivates abnormal clock genes and supplementary chronotherapies and medications can block relapse and stabilize circadian-related improvement (Bunney and Bunney 2013).

Antidepressant medications are a shared precipitant in both disorders. Antidepressants lower the seizure threshold but the mechanisms by which they may cause mood elevation are not well understood. It is hypothesized that in BD several neurobiological factors are associated with spontaneous and treatment-emergent mood episode switches, including abnormalities in catecholamine levels, upregulation of neurotrophic and neuroplastic factors, HPA-axis hyperactivity and circadian rhythms (Salvadore, Quiroz et al. 2010). A recent study assessed the risk of first-episode seizures in patients with depressive disorder and concluded that SSRI and SNRI antidepressants are associated with an increased risk of seizures (Blöchliger, Ceschi et al. 2015).

6.1.2 Neurocognition

It is unclear to what extent BD is best defined by acute signs and symptoms of illness episodes and to what extent BD may relate to inter episode brain vulnerabilities or damage secondary to illness episodes. This may be examined in terms of neurocognitive trait markers in euthymic BD and in TLE during seizure-free intervals. The findings in chapter 3 indicated that deficits in BD-I, compared to healthy controls, were in the three domains of executive function, attention span and verbal memory. Deficits specific to TLE compared to healthy controls included executive function and memory. Both disorders had deficits in executive function and verbal memory which implicated the frontal lobes and the temporal lobes.

6.1.3 The ketogenic diet

There is a well-established overlap in treatments for BD and epilepsy, particularly with mood stabilizer medications such as sodium valproate. The search for commonalities between BD and epilepsy led to a review of the application to mental disorders of an evidence-based treatment for epilepsy, the ketogenic diet (KD). The use of KD in mental disorders was presented in chapter 4. Fifteen studies (9 animal models, four

human case studies and two uncontrolled trials) examined the use of KD in anxiety, depression, bipolar disorder, schizophrenia, autism (ASD) and attention deficit hyperactivity disorder (ADHD). Whilst the pathophysiology of these mental disorders is not clearly understood and the literature is in a formative stage, a number of actions have been postulated for an effect of KD on mental disorders, including mitochondrial function, neurotransmitter changes and through the reduction of intra-cellular calcium. Mitochondrial dysfunction may be relevant in some mental disorders including schizophrenia, ASD, and ADHD, however there is no clear established link to BD. Improvements seen in anxiety, depression, and bipolar disorder may be related to alterations of neurotransmitters whilst patients are on the diet. In BD, a mechanism by which KD may be effective is based on the hypothesis that acidosis achieved through ketosis reduces intra-cellular sodium and calcium, both of which are elevated in this disorder. It is noted that mood stabilizers have a similar effect, reducing intra-cellular sodium in an activity-dependent manner, through acidification of the blood. A recent systematic review and meta-analysis of clinical studies of the kynurenine pathway in mood disorders reported that, contrary to previous reports, KYNA is decreased in major depression (Arnone et al., 2018). This opens the possibility that KD has a yet unproven anti-depressant effect mediated by increased KYNA.

6.1.4 Mania associated with herbal medicine

The aim of the research presented in Chapter 5 was to review published reports of mania associated with herbal medicine other than cannabis. This examined the diagnostic category of substance/medication-induced bipolar and related disorder to illustrate its potential use in understanding the varied pathophysiology of mania. There were no randomized controlled trials on this subject. The study sample consisted of 35 case reports published as 19 single and 7 multiple case reports. Putative pathophysiological

mechanisms were postulated for nine of the 11 herbal medicines reported and centred on HPA-axis activation and increased monoamine activity.

6.2 Limitations

Limitations discussed include the use of review methodologies, comparison with a reference condition, and specific limitations from the individual studies including retrospective accounts.

6.2.1 Review methodologies: narrative review and systematic review

Narrative review

Narrative reviews are generally comprehensive and include a wide range of issues within a given topic but typically do not state or follow rules for the search of relevant evidence (Collins and Fauser 2005). The primary aim of a narrative review is to provide the reader with a comprehensive background for understanding current knowledge and highlighting the significance of new research (Cronin, Ryan et al. 2008). The studies on precipitating factors for mania and seizures (chapter 2) and the ketogenic diet in mental disorders (chapter 4) were completed using narrative review methodology as they sought to merge a broad body of research together in a cohesive format.

Unlike systematic reviews, narrative reviews are considered to be one of the weakest forms of evidence to use in clinical decision making as they often deal with a broader issue rather than focused clinical problems (Green, Johnson et al. 2006). However, they may be useful for the generation of hypotheses on a given topic. This thesis was not directed at clinical-decision making but rather the generation of leads in the understanding of the underlying causes and pathways of mania, including those drawn from the comparison with temporal lobe epilepsy.

Systematic review

Systematic reviews are at the forefront of evidence-based medicine. They involve the process of systematically finding, appraising and using research findings as the basis of clinical-decision making (Rosenberg and Donald 1995). They constitute a rigorous and transparent form of literature review (Mallett, Hagen-Zanker et al. 2012) and involve the identification, synthesis and assessment of available information. In 2009, the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement was published (Moher, Liberati et al. 2009). This was devised to ensure that authors provided a transparent and complete reporting of this type of review. In this thesis, systematic review methodology has been applied in the studies on neurocognition (chapter 3) and mania associated with herbal medicine (chapter 5).

However systematic review methodology presents some disadvantages including publication bias whereby small or non-significant studies often fail to reach publication and are therefore not considered in the review process (Biondi-Zoccai, Lotrionte et al. 2011). Another limitation is that systematic reviews are often restricted to English language articles which may potentially lead to the omission of important findings in other languages. This may have been particularly problematic in the systematic review of mania associated with herbal medicine (chapter 5) which excluded literature from studies written in languages other than English, whereas the use of herbal medicine is well established in different cultures and reported in various language sources.

While systematic reviews are more appropriate for focused topics and traditional narrative reviews are better suited to comprehensive topics, either approach can be adapted to clinical or scientific avenues of enquiry (Collins and Fauser 2005).

6.2.2 Comparison with a reference condition

The use of a reference condition to compare disorders which share some common features is a method that has been applied to conditions such as schizophrenia and TLE (Gold, Hermann et al. 1994) and migraine and epilepsy (Haut, Bigal et al. 2006). In this thesis, the basis for comparing BD and TLE was the recognition that there were a variety of features in common such that research findings in the two conditions might usefully be considered in framing hypotheses about pathogenesis and pathophysiology of either. This is particularly so with reference to the localizing pathology in TLE and the overlap in treatments targeting the central nervous system. However, as indicated throughout this thesis the relationship between the two disorders is complex. Similarity does not prove that underlying processes are identical. Thus, common surface features may derive from different underlying neuroanatomical pathways or neurophysiological processes. However, similarities, as with associations in general, are useful in framing hypotheses based on a presumption of shared mechanisms.

6.2.3 Limitations of the individual studies

Each of the four publications presented in chapters 2-5 includes a section on limitations specific to that study, the following comments are additional to these. In the study of precipitating factors (chapter 2) the literature relies heavily on retrospective accounts. These may be influenced by forgetting, remembering events as having occurred earlier than was the case and reinventing the past to suit their current needs and circumstances (Henry, Moffitt et al. 1994).

The overview of the literature on neuropsychology in BD-I and TLE (chapter 3) is limited by the differences in experimental methodologies which prevented a meta-analytical approach. Some medications may have a deleterious effect on cognition. This was not routinely reported or controlled in analyses in either BD or TLE. Other

extraneous variables that were not systematically considered in the literature included the time elapsed between mania or seizure episodes and neuropsychological testing, number of hospitalizations and the presence of psychotic symptoms. The experimental designs employed in the studies in BD-I and TLE reflected different lines of enquiry. The BD-I literature routinely included a healthy control group whereas the TLE controlled trials used patients as their own controls pre- and post-ablative surgery. This fundamental difference in design meant that the two conditions could not be directly compared using meta-analytic techniques.

In the review of KD studies (chapter 4), sample sizes were small (range 1-30) and there was no control for placebo effects. Confirmation of the establishment of ketosis (an important marker for the diet's effect on metabolism) was not reported in three human studies. Adherence to the diet is limited by the need to follow a detailed regimen, often unpalatable food choices, gastrointestinal side effects and the duration of the diet required. In humans, what constitutes KD is varied with no uniform standards of lipid:non-lipid ratios.

It is difficult to establish whether the episodes of mania associated with herbal medicine (chapter 5) were causally linked or coincidental. The literature is insufficient in depth and case reports do not permit inferences regarding causality to be tested in depth. Case reports are also subject to confirmation bias, the tendency for authors to investigate a subject in conformity with existing beliefs as to causation.

6.3 Directions for future research

This thesis is primarily concerned with the aetiology of mania as a manifestation of bipolar disorder. The review papers aim to identify research findings from the published literature that may provide clues to directions in research that may yield an increased

understanding of the pathogenesis and pathophysiology of mania and potentially aid in the search for improved treatments.

The use of temporal lobe epilepsy as a reference condition has identified a number of overlaps with mania in clinical features, course, precipitants, cognitive deficits and treatment response. These lend themselves to further investigation in a number of ways, examples of which are presented below. These examples are based on head-to-head comparison of clinical samples of mania and TLE, comparing and contrasting the two conditions. Variables considered are precipitating factors including self-induction of manic and seizure episodes respectively, neurocognition, olfactory functioning and facial affect processing. In addition, potential further research on the ketogenic diet in BD is canvassed. Finally, the possibilities of population-wide screening for adverse reactions to herbal medicines in both mania and temporal lobe seizures are discussed with reference to the potential application of data mining using natural language processing techniques.

Previous research has used different instruments and methodologies to investigate precipitating factors for mania in BD and seizures in TLE, examining each disorder in isolation. A direct comparison incorporating a questionnaire on precipitating factors developed for use in both conditions would yield higher quality comparative information. Further, given the unpredictable nature of episodes in both TLE and BD, a comparison of precipitating factors in the two disorders using prospective methodology involving seizure or mania diaries would strengthen the evidence as to what constitutes precipitants in common. An increased understanding of precipitating factors may lead to biological, psychological or social interventions to arrest episodes in the prodromal phase thus leading to a better quality of life for patients.

In epilepsy, self-induction of seizures is a well recognised phenomenon, for example waving a hand in front of the eyes to produce a flickering effect in photosensitive epilepsy. Typically, this involves an irresistible, compulsive attraction which precipitates seizure activity and interferes with social and occupational functioning (Rektor, Schachter et al. 2013). Patients report engaging in these forms of behaviour for a variety of motives including a pleasant feeling, a reduction in stress or to avoid obligations (Binnie 1987). Case-reports have been published on self-induction in various forms of reflex epilepsy (Binnie 1987), for example hand clapping (Van der Meij, Franssen et al. 1997) and listening to music (Klass 1989). There is a correlation between the pleasure that has been felt from a seizure and a person's ability to induce seizures (Faught, Falgout et al. 1986). Patients with self-induced seizures are often resistant to traditional therapy; in these instances, seizures may be modifiable by behavioural or psychiatric intervention (Ng 2002).

Self-induction of mania is a little explored aspect of the condition but may be a relevant form of precipitant. Participants in online consumer forums sometimes report using staying up late and consuming energy drinks as ways of bringing on highs. A case report described self-induction of mania using cough syrup (Mendez 1992). Another, often repeated, observation noted that "patients may discontinue the prophylactic use of lithium as they do not want to be deprived of their periodic hypomania" (Van Putten 1975). Survey data comparing patients with BD and TLE on both open-ended questions and questionnaire responses regarding self-induction methods may assist in delineating the phenomenon.

With respect to neurocognition, head-to-head comparison of the neuropsychological deficits between the two disorders may improve understanding of the neural substrates of the two disorders. This would include individuals with a

diagnosis of: bipolar disorder type I (BD-I), left-sided temporal lobe epilepsy, right-sided temporal lobe epilepsy and healthy matched control participants (HC). A targeted test battery would include tests of executive function, verbal memory and non-verbal memory coupled. Further information would be obtained by using functional magnetic resonance imaging to indicate areas of task relevant neural activation.

Comparing BD and TLE on olfactory function could be a potentially fruitful line of research. In both humans and non-human animals, sense of smell represents an important arousal system that brings attention to environmental events, air quality and food (Engen 1983). The inferior frontal and temporal lobes are particularly implicated in human olfactory processing (Zatorre 1992). It may be expected that BD and TLE would have an effect on olfactory function. Eskenazi et al. (1986) found bilateral impairment in odour identification in patients with TLE (Eskenazi, Cain et al. 1986). Using the University of Pennsylvania Smell Identification Test (UPSIT) Kohler et al. compared olfactory dysfunction in schizophrenia and TLE (Kohler, Moberg et al. 2001). The results showed that patients with schizophrenia and those with right TLE were impaired in smell recognition when compared to healthy participants. In a comparison of patients with left TLE and right TLE, the latter had difficulty matching smells to the stimulus (Hudry, Perrin et al. 2003). TLE patients were impaired on the UPSIT relative to HC; impairment was not related to laterality of seizure focus, duration of seizure, baseline seizure control or number of medications (Desai, Agadi et al. 2015).

There are relatively few studies on olfactory function in BD-I (Hardy 2012). Comparison of patients with BD-I to SZ, found UPSIT deficits in both groups with a larger effect size in SZ (Cumming, Matthews et al. 2011). Hardy et al. compared right and left nostril sensitivity for odour detection and smell identification in 20 patients with BD-I relative to 44 HC. Smell identification was normal in BD-I, symptoms of

depression were related to hyperacuity and symptoms of mania to hypoacuity of smells (Hardy 2012). In interepisode (euthymic) patients with BD-I, mood episodes triggered by emotional events were associated with heightened olfactory function relative to episodes without emotional triggers (Kruger, Frasnelli et al. 2006). These inconsistent findings in BD warrant future research into olfactory function.

Facial affect processing is another point of comparison between BD and TLE. The recognition of emotion utilizes a distributed set of structures, including the occipitotemporal neocortex, amygdala, orbitofrontal and right frontoparietal cortices (Adolphs 2002). The processing of facial affect is important for socialization and social interaction (Corden, Critchley et al. 2006). One method to examine emotion perception is through studies of facial affect recognition.

In epilepsy, psychosocial maladjustment is common (Hermann, Seidenberg et al. 2000). Childhood and early onset right TLE are associated with poor recognition of emotional facial expressions, in particular fear (Meletti, Benuzzi et al. 2003, Golouboff, Fiori et al. 2008). In another study, participants with TLE relative to HC were impaired in the recognition of all facial expressions except happiness (Meletti, Benuzzi et al. 2009). A degree of laterality has been found. Patients with right TLE were more impaired that those with left TLE (Meletti, Benuzzi et al. 2009).

In BD-I relative to HC participants, manic patients with BD-I, were impaired on a task of facial affect labelling (Getz, Shear et al. 2003). In another study, patients with BD-I showed worse recognition of facial affect than HC, in particular identifying fear and disgust (Lembke 2002). A direct comparison of BD and TLE would provide further information regarding the similarities and differences in deficits of emotion perception in the two disorders particularly in the euthymic and interictal phases of these disorders.

The ketogenic diet requires further research to clarify the specifics of dietary manipulation or ketone supplementation necessary to produce optimum ketosis using open-label studies and randomized controlled trials. Careful attention should be given to measuring ketone levels in either the urine or blood in both murine and human trials. Whilst adherence to KD can be confirmed by ketone levels, the diet is difficult to follow. The advent of an exogenous ketone supplement (AC-1202), taken on a standard diet, opens opportunities for more precise placebo-controlled research in humans to confirm or disconfirm its applicability. Research on exogenous ketone supplements is underway, for example the clinical trials register of the United States National Library of Medicine lists ‘a Study to Compare the Pharmacokinetics of AC-1202 and Two Doses of AC-SD-01 on Ketone Body Production’ was recently registered (NCT03063645, 24 February 2018).

The systematic review of herbal medicine associated mania presented in chapter 5 indicates that evidence is limited to case reports. Nevertheless, the findings suggest that herbal medicines may not be as innocuous as previously thought.

New information technology techniques are emerging that assist in detecting associations between variables pertaining to medication use and mental disorders. Examples include the extraction of meaningful clinical summary information from electronic health records (EHRs) using natural language processing algorithms. In future, linked data might include purchases of herbal medicines, online searches on relevant health topics or reports of side effects or illness exacerbations in online forums. Further work is required to establish firm ethical protocols before such research can meet its potential. A full discussion of this area is outside the scope of this thesis, however recent studies in the mental health field indicate the applicability of such methods to studies of symptoms, substance use and mental health outcomes in large

clinical populations. Examples using EHRs include a study of mood instability as a prognostic factor (Patel, Lloyd et al. 2015), ascertainment of tobacco use status (Hegde, Shimpi et al. 2018) and derivation of diagnostic phenotyping (Castro, Minnier et al. 2015).

The research presented in this thesis emphasizes the work of many thousands of researchers over decades, which in summary form provides some indication of ways forward in the quest to both understand and remedy the manifestations of bipolar disorder. With research proceeding on many broad fronts there is every reason to be confident that such an understanding can be reached through the application of insights, hypotheses and methodologies combined with careful and systematic investigation.

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Appendix A
Coding Manual Chapter 3
Systematic Review of Cognitive Function in Euthymic Bipolar Disorder and Pre-Surgical Temporal Lobe Epilepsy

Coding Manual: Systematic Review of Cognitive Function in Euthymic Bipolar Disorder and Pre-Surgical Temporal Lobe Epilepsy

Prepared by Emmanuelle C. S. Bostock, 2015

To ensure reliability of coding, articles should be classified using the "*Coding Sheet Study ID: EB15"* as per the following instructions:

At the top right hand corner of each page a "Sheet ID number" should be allocated to each publication assessed. The first publication will be marked "15EB001", the second 15EB002 etc. This should be marked on the top right hand corner of each page.

1. Article ID No:

An article identification number should be included under **"Article ID No.".** The ID is specified in BLOCK CAPITALS. It is comprised of:

- the surname and the initials of the first author
- the publication year
- the surname of the second author (if no secondary author: xx)
- the MEDLINE abbreviation of the journal (or in full if not available) in which it was published
    - e.g., BOSTOCK E C S KIRKBY K C ET AL 2015 J AFFECT DIS
    - or BOSTOCK E C S 2014 XX J AFFECT DIS

2. Bipolar Disorder/Focal seizures

- Coder is to clearly indicate which disorder the article pertained to by circling, if both then circle one and complete two coding sheets.

3. Title and abstract screening:

Indicate by checking the box ☒ for YES or NO under each criterion listed below:

YES ❒ NO ❒ Published 1980 or later

YES ❒ NO ❒ Included humans

YES ❒ NO ❒ Adult participants (18 years or over)

YES ❒ NO ❒ Examined at least one neuropsychological construct

YES ❒ NO ❒ Full article in English

4. Full text screening:

YES ❒ NO ❒ Study included euthymic bipolar disorder participants

YES ❒ NO ❒ Focal seizures arising from the temporal lobes

YES ❒ NO ❒ Participants were judged as euthymic by a clinician

YES ❒ NO ❒ Participants had a Young Mania Rating Scale below 8

YES ❒ NO ❒ Participants had a Hamilton Depresssion Rating scale above 8

YES ❒ NO ❒ Participants had a brain lesion

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5. Actions arising:

Study will be included: This should be checked when the coder has decided that the inclusion criteria have been met.

Study will be excluded: A coding sheet must be created for any excluded study. However, it is sufficient to only fill in the first page of the coding sheet and the **general publication information** section.

Multiple coding sheets: If both **bipolar disorder** and **focal seizures** are examined in a single publication, an individual coding sheet is filled out for each.

Write to authors: This should be checked in situations where the manuscript did not contain sufficient information

6. General Publication Information:

Coder: Enter the initials of the coder (e.g., Emmanuelle Bostock = EB)

Coding date: Day/ Month/ Year

Time of day: specify the start time in order to determine the total duration of coding.

Authors: Specify the last name of the first three authors. If more than three authors are mentioned, all the other authors are abbreviated with et al. The publication year is four digits (e.g., Bostock, Kirkby, Garry et al., 2015).

Title: Note the first six words from the title e.g., "*Comparison of precipitating factors of mania and partial seizures: Indicative of shared pathophysiology*" becomes - "*Comparison of precipitating factors of mania"*

Country of Origin - Author: of the first author is usually noted on the publication. If not, it should be Googled and entered using the codes below. If the author has more than one Country of Origin enter this as Other Origin.

Coding of Country of Origin:

1 = USA
2 = Canada
3 = Germany
4 = Great Britain
5 = Netherlands
6 = Scandinavia
7 = Australia
8 = Western Europe (excluding G, GB, N, S)
9 = Eastern Europe (including Russia)
99 = Other (Specify)

Discipline of the first author: This is usually noted on the publication. If not it should be Googled and entered using the codes below. If the author has more than one discipline listed, this should be entered under other discipline.

Coding of Discipline:

1 = Psychology
2 = Psychiatry
3 = Medicine
4 = Sociology
5 = Economy
6 = Education
99 = Other

Publication found in: The source of the publication should be entered as follows

1 = Scopus
2 = Web of Science
3 = PubMed
4 = PsychINFO
5 = Google Scholar
6 = Manual search of journals
7 = Hand search of reference lists
8 = Contact with authors
99 = Other source

Note: Some publications may appear in more than one database. The code given will reflect the first place where the publication was found by the coder.

Coding the type of publication:

1 = Journal with peer review
2 = Journal without peer review
3 = Book/ book chapters
4 = Dissertation (PhD)
5 = Honours or Master's thesis
6 = Conference presentation/ Poster (Abstract or full paper)
7 = Unpublished manuscript
8 = Internet document
99 = Other

Citations: How many citations does the study have?

Impact: What is the impact factor of the journal?

7. Description of the study:

The experimental design (i.e., between groups, within groups or mixed designs) or the publication type (i.e.,literature review, narrative review or meta-analysis) should be clearly indicated by ticking the box next to the study design.

8. Sample Information:

Sample size: refers to the total amount of participants in the study.

Illness: Should be clearly indicated whether the study examined BD or FS even though there is a separate coding sheet for each.

Illness Phase: Can refer to mania, depression, euthymia. Interictal, periictal or postictal phases.

YMRS Mean Score and HamD Mean Score:

Bipolar illness phases has been adopted from Arts, Jabben, Krabbendam and van Os (2008) who conducted a meta-analysis of euthymic patients. Studies should be coded as per the categories below:

Euthymia is defined as:

- judged as euthymic by a clinician
- >8 on the Hamilton Depression Rating Scale
- <8 on the Young Mania Rating Scale
- and/or a score on mood rating scales below this point

Duration of illness years: Should be recorded as a mean for the whole sample

Age at Onset of illness: If indicated in the study, record information here regarding at what age participants were diagnosed with either BD or FS if known (in months).

Whereby:

M: Mean value.

SD: Standard deviation.

Males: the mean number of males in the sample Females: the mean number of females in the sample

Age: The mean, standard deviation and Range: Specify a minimum and maximum Age at the time of testing

Education in years: should be recorded as a mean of the total sample

Coding of Ethnicity: Ethnicity is specified only if the proportion of this ethnic group makes up a minimum of 50% of the sample.

1 = White (Caucasian, Anglo-American, European)

2 = Black

3 = Hispanic

4 = Indigenous People

5 = Asian

6 = Mixed (when two ethnic groups are represented with 50% each)

99 = Other (specify)

Coding of Country of Origin

Specify in which Country the study was conducted.

1 = USA
2 = Canada
3 = Germany
4 = Great Britain
5 = Netherlands
6 = Scandinavia
7 = Australia
8 = Western Europe (excluding G, GB, N, Scandinavia)
9 = Eastern Europe (including Russia)

99 = Other (Specify)

Medications: should be listed in the section provided.

Seizure frequency: The mean number of seizures prior to assessment should be recorded as means and standard deviations.

Surgical Procedure:

Focal seizures arising from the temporal lobes: Also known as temporal lobe epilepsy and partial seizures arising from the temporal lobes:

- participants' cognitive abilities were assessed prior to selective
  - amygdalahippocampectomy or
  - anterior temporal lobectomy

Decimal Places

All *sample values* should be a maximum of two decimal places (rounded).
All *statistical values* should be a maximum of three decimal places.

9. Dependent Variables

The dependent variable/s examined should be listed under the category.

If the publication examined several **dependent variables** (including separate subscales) (e.g. WAIS, RAVLT), each dependent variable is listed.

10. Concluding Information

At the end of coding an article, the time needed for encoding should be noted.
In addition, there is space for problems and comments. If information is missing, the missing information should be listed here.

Finally, include a brief interpretation of the study in this box. This can be transcribed or taken directly from the publication abstract.

Appendix 1: Neuropsychological Measures used by other meta-analyses on euthymic BD

Neuropsychological Measures Assessed: Kurtz & Gerraty (2009)

Test
Attention
Continuous Performance Test
Digits Forward
Trails A
Working Memory
Digits Backward
Verbal Memory
Rey Auditory/California Verbal Learning Test – Total recalled, long-delay Free recall
Wechsler Memory Scale-logical Memory (WMS-LM)
Nonverbal Memory
Rey Complete Figure Test (RCFT) – Immediate and delayed recall
Wechsler Memory Scale-Visual Reproduction (WMS-VR)
Visuospatial function
Block design
Rey Complex Figure Test (RCFT)-copy
Language
Controlled Oral Work Association Test (COWA-FAS)
Animal Naming (AN)
Psychomotor speed
Digit Symbol Substitution Test (DSST)
Executive –function
Wisconsin Card Sorting Test (WCST) – Categories achieved and Perseverative errors
Stroop Color Word Test (SCWT)
Trails B

Congintive Battery Mann-Worbel & Carreno (2011)

Cognitive domain
Processing speed
Digit Symbol
Trails A
Stroop Word
Stroop Color
Haylings A (sec)
Average effect size
Executive functioning
WCST categories
WCST perseverative errors
Trails B
Stroop interference
Haylings B (sec)
Haylings B (errors)
Average effect size

Working Memory
Digit Span-forward
Digit Span-backward
Digit Span-total
Visual Span-backward
Average effect size

Perceptual/problem solving
Block design
Figure Copy
Average effect size

Intellectual/verbal
Vocabulary
Word Reading
Average effect size

Neuropsychological Battery: Robinson, Thompson et al. (2006)

Test
Intelligence and education
IQ
Years of education
Executive measures
Category Fluency
Reverse Digit Span
Trail Making Test B
WCST perseverations
Verbal Fluency (FAS)
Verbal learning and memory measures
A/CVLT total recall trails 1-5
A/CVLT short delay free recall
A/CVLT long delay free recall
Forward digit span
Attention and psychomotor speed
Sustained attn: latency
DSST
Trail Making Test A
Sustained attn: sensitivity

Neuropsychological battery: Torres, Boudreau et al., (2007)

Table1. Most frequently employed tasks in studies of euthymic bipolar patients

Task by cognitive domain
Premorbid intellectual
Single-work reading score from NAART, WRAT
WAIS vocabulary subset score
Attention/processing speed
Trail making Test A: completion time
Digit Symbol or Symbol Digit Modalities Test score
CPT* or variant: accuracy (hits)
CPT* or variant reaction time
Memory

Learning (recall trails 1-5) from CVLT, RAVLT
Short delayed recall from CVLT, RAVLT
Long delayed recall from CVLT, RAVLT
Recognition hits from CVLT, RAVLT
Executive/working memory
Digit span backward or total forward and backward
Trail making Test B: completion time
WCST: Total Categories score
Verbal Letter Fluency (3 trails): number correct
Stroop interference trail, number correct, or interference score

NAART, North America Adult Reading Test; WRAT, Wide Range Achievement Test; WAIS, Wechsler Adult Intelligence Scale; CPT, Continuous Performance Test; WCST, Wisconsin Card Sorting Test.
*When multiple CPT tasks were used within a given study, the simplest, non-working memory versions was employed.

Neuropsychological Test battery: Arts, Jabben., (2008)

Test
Digit Backward
Trail B
WCST perseverative errors
Fluency categories
CVLT delayed recall
DSST
CVLT immediate recall
Stroop Correct
Rey figure recall
FAS
CPT correct
WCST categories
Digit forward
Rey copy
IQ

Neuropsychological Test Battery: Bora, Yucel (2009)

Table 3
Mean weighted effect sizes for individual tasks and education for patient-control differences

Test
TMT-B
Verbal learning
CPT omission
Delayed recall
Stroop
DSST
Digit span backwards
Immediate recall
WCST per
TMT-A
WCST Cat
FAS
Visual memory recall
Verbal recognition
Current IQ
Digit span Forward
CPT commission
Visual copy
IQ premorbid

Appendix B
Coding Sheet
Systematic Review of Cognitive Function in Euthymic Bipolar Disorder and Pre-Surgical Temporal Lobe Epilepsy

Coding Sheet Study ID: EB15

Systematic Review of Cognitive Function in Euthymic Bipolar Disorder and Pre-Surgical Temporal Lobe Epilepsy

1. Article ID No:

---

2. (circle) **Bipolar Disorder** **Focal seizures**

---

3. Title and abstract screening:

YES ❒ NO ❒ Published 1980 or later

YES ❒ NO ❒ Included humans

YES ❒ NO ❒ Adult participants (18 years or over)

YES ❒ NO ❒ Examined at least one neuropsychological construct

YES ❒ NO ❒ Used a quantitative design

YES ❒ NO ❒ Full article in English

4. Full text screening:

YES ❒ NO ❒ Study included euthymic bipolar disorder type I participants

YES ❒ NO ❒ Focal seizures arising from the temporal lobes

YES ❒ NO ❒ Participants were judged as euthymic by a clinician

YES ❒ NO ❒ Participants had a Young Mania Rating Scale below 8

YES ❒ NO ❒ Participants had a Hamilton Depresssion Rating scale above 8

YES ❒ NO ❒ Participants had a brain lesion

---

5. Actions arising:

❒ Study will be included ❒ Write to authors

❒ Study will be excluded ❒ Multiple coding sheet

6. General Publication Information:

Coder: _____ Coding Date ___ / ___ / _____ Time of Day: _____

Authors: _____

Publication Year: _____

Title (first six words): _____

Country of Origin - Author: _____

Other Origin: _____

Discipline of the First Author: _____

Other Discipline:_____

Publication Found In: _____

Other Place Publication Found: _____

Type of Publication: _____

Other Publication: _____

Citations: _____

Impact: _____

7. Description of the Study

Experimental:

❒ Between groups

❒ Within Groups

❒ Mixed

❒ Literature review

❒ Narrative review

❒ Meta-analysis

---

8. Sample Information:

Sample Size _____

Illness (Circle) Bipolar Disorder Focal Seizures Other

Illness Phase: _____

YMRS Mean Score_____

HamD Mean Score: _____

Clinician rated as euthymic: _____

Duration of illness years:_____

Age at Onset of illness : M = _____SD= _____

Males *N*=_____Females *N*=_____

Age: *M* = _____ *SD* = _____ Range from _____ to _____

Education (years):_____

Ethnicity: ____ Other Ethnicity: ____ Country of Origin: ____ Other Country of Origin:

Medication : _____

Seizure frequency: _____

Surgical Procedure: _____

9. Dependent variables

DV1: _____
DV2:_____
DV3:_____
DV4:_____
DV5:_____
DV6:_____
DV7:_____
DV8:_____
DV9:_____
DV10:_____

10. Concluding Information

Time for Coding: _____ Minutes: _____

Problems/Comments: _____

Study Interpretation: _____

Appendix C
Coding Manual
Mania associated with herbal medicines, other than cannabis: a systematic review and quality assessment of case reports

Coding Manual: Herbal medicines, other than cannabis, associated mania: A systematic review

Authors: Emmanuelle C. S. Bostock, Kenneth C. Kirkby, Michael I. Garry, Bruce V. M. Taylor & Jason, A. Hawrelak

2017

Article ID No:

At the top of each page of the coding sheet fill in the sheet ID number and also number the printed article (e.g., article 1, article 2).

An article identification number should be included under **"Article ID No."**.

The 7-digit ID is specified in BLOCK CAPITALS. It is composed of:

- the first three letters of the surname of the first author
- If the first author's last name is two letters long a lower case z will be inserted after the first two letters (e.g., Author HO becomes HOz)
- the last two digits of the publication year (e.g., 2017 becomes 17)
- the first two letters of the surname of the second author (if no secondary author: xx)
- e.g., Qureshi, N. A., & Al-Bedah, A. M. (2013). Mood disorders and complementary and alternative medicines: a literature review. *Neuropsychiatric Disease and Treatment, 9,* 639-658.
- Is coded as the following: QUR13AL

Title and Abstract Screening:

Tick "YES" or "NO" for each of the inclusion criteria (e.g., inclusion criterion (a) is that articles must be published after 1980, therefore if an article has been published on the topic of interest in 1979 it is excluded thus leading the reviewer to select "NO")

Exclusion Criteria

If one of the following criteria apply, the study must be excluded:

1. Published prior to 1980
2. Included children (<18 years old) due to the generally agreed upon age of informed consent
3. Was not peer-reviewed
4. Was in a language other than English, as this is the scientific language
5. Did not include a diagnosis of bipolar disorder or related disorder

For excluded studies it is sufficient to only fill in the **general publication information** section. In addition, the **"Excluded"** box should be ticked and reasons should be provided in the comments box on the last page.

NOTE: *CLARIFY:* This should be checked in situations where the manuscript did not contain sufficient information.

> The type of bipolar disorder should be specified either bipolar type I, bipolar type II, Substance/medication-induced bipolar and related disorder, cyclothymia, mixed sample of BD, animal analogue of BD

General Publication Information:

Coder: Enter the initials of the coder (e.g., Emmanuelle Bostock = EB)

Coding date: Day/ Month/ Year

Time of day: specify the starting time in order to determine the total duration of coding.

Authors: Specify the last name of the first three authors. If more than three authors are mentioned, all the other authors are abbreviated with et al. The publication year is four digits (e.g., Bostock, Kirkby, Garry et al., 2015).

Publication Year: Specify the date the article was published (e.g., 2015).

Title: Note the first six words from the title (e.g., "*Comparison of precipitating factors of mania and partial seizures: Indicative of shared pathophysiology*" becomes - "*Comparison of precipitating factors of mania")*

Country of Origin: of the first author is usually noted on the publication. If not, it should be Googled and entered using the codes below. If the author has more than one Country of Origin enter this as Other Origin.

Coding of Country of Origin:

1 = USA
2 = Canada
3 = Germany
4 = Great Britain
5 = Netherlands
6 = Scandinavia
7 = Australia
8 = Western Europe (excluding G, GB, N, S)
9 = Eastern Europe (including Russia)
99 = Other (Specify)

Discipline of first author: This is usually noted on the publication. If not it should be Googled and entered using the codes below. If the author has more than one discipline listed, this should be entered under other discipline.

Coding of Discipline:

1 = Psychology
2 = Psychiatry
3 = Medicine
4 = Allied Health
99 = Other

Publication found in: The coding of where the publication was found should be entered as follows:

1 = PubMED
2 = EMBASE
3 = CINAHL
4 = Health Source
5 = PsychInfo
6 = Hand search of reference lists
7 = Contact with authors
99 = Other source

Note: Some publications may appear in more than one database. The code given will reflect the database that has remained after duplicates have been removed.

Coding the type of publication:
1 = Journal with peer review
2 = Journal without peer review
3 = Book/ book chapters
4 = Dissertation (PhD)
5 = Honours or Master's thesis
6 = Conference presentation/ Poster (Abstract or full paper)
7 = Unpublished manuscript
8 = Internet document
99 = Other

Description of the study:
If experimental the design should be marked (i.e., between groups, within groups, mixed designs, case study, case series) or if the publication is a literature review, narrative review or meta-analysis that should be clearly indicated.

Sample Information:

Sample size: Record the sample size listed in publication

Illness: Should be clearly indicated whether the study examined BD or another illness, please note that mania that has occurred secondary to infection, neoplasm, epilepsy and metabolic disturbances are excluded. However mania that has arisen from a CAM intervention is included.

Coding of Illness Phase: Are the participants in the study (a) hypomanic (b) manic (c) depressed or (d) euthymic.

- NOTE: Given that we are interested in the bipolar spectrum in any phase of the disorder we are not applying strict criteria for euthymia as we have done in other papers as some of the participants are self-reported as having bipolar disorder.

Duration of illness years: List if specified

- M: Mean value.
- SD: Standard deviation.
- Range: Specify a minimum and maximum.

Age at Onset of illness: Record information here regarding at which age participants were diagnosed with BD

Males and Females: Should be filled in.

Age: at time of testing.

Education: Should be recorded in years

Coding of Ethnicity

1 = White (Caucasian, Anglo-American, European)
2 = Black
3 = Hispanic
4 = Indigenous People
5 = Asian
6 = Mixed (when two ethnic groups are represented with 50% each)
99 = Other (specify)

Coding of Country of Origin

Specify in which Country the study was conducted.

1 = USA
2 = Canada
3 = Germany
4 = Great Britain
5 = Netherlands
6 = Scandinavia
7 = Australia
8 = Western Europe (excluding G, GB, N, Scandinavia)
9 = Eastern Europe (including Russia)
99 = Other (Specify)

Medication: List current medication of participants if known.

Concluding Information:

At the end of coding an article, the time taken should be noted.

In addition, there is space for problems and comments.

Finally, include a brief interpretation of the study. This can be transcribed or taken directly from the publication abstract.

Appendix D
Coding Sheet
Mania associated with herbal medicines, other than cannabis: A systematic review of case reports

Coding Sheet Study ID: EB17REV

Mania associated with herbal medicines, other than cannabis: A systematic review of case reports

Article ID No:

Title and abstract screening:

1. YES ❒ NO ❒ Published 1980 or later
2. YES ❒ NO ❒ Only adult participants (18 years or over)
3. YES ❒ NO ❒ Peer-reviewed
4. YES ❒ NO ❒ Full article in English
5. YES ❒ NO ❒ CLARIFY ❒ Diagnosis of bipolar disorder or related disorder.
6. YES ❒ NO ❒ Review article
7. YES ❒ NO ❒ on cannabis

Actions arising:

Include all five YES ❒

Excluded any NO ❒

CLARIFY **Write to authors** ❒

Specify type of bipolar disorder:

❒ bipolar type I, OR
❒ bipolar type II, OR
❒ Substance/medication-induced bipolar and related disorder
❒ cyclothymia
❒ mixed sample of BD
❒ animal analogue of BD

General Publication Information:

Coder: _____ Coding Date ___ / ___ / _____ Time of Day: _____

Authors: _____

Publication Year: _____

Title (first six words): _____

Country of Origin - Author: _____

Other Origin: _____

Discipline of the First Author: _____

Other Discipline:_____

Publication Found In: _____

Type of Publication: _____

Description of the Study

Experimental:

❒ Between groups

❒ Within Groups

❒ Mixed

❒ Case study

❒ Case series

❒ Literature review

❒ Narrative review

❒ Meta-analysis

Sample Information:

Sample Size _____

Illness (Circle) Bipolar Disorder Other

Illness Phase: _____

CAM Modality used (if several list all):_____

Duration of illness years:_____

Age at Onset of illness : M =_____SD=_____Range=_____

Males *N*=_____Females *N*=_____

Age: *M* = _____ *SD* = _____ Range from _____ to _____

Education (years):_____

Ethnicity: ____ Other Ethnicity: ____ Country of Origin: ____ Other Country of Origin:

Medication : _____

Concluding Information

Time for Coding: _____

Problems/Comments: _____

Study Interpretation: _____

Appendix E
Quality Assessment Scale by Agbabiaka

Appendix A. Quality Assessment Scale by Agbabiaka
Category/questions Rating (please tick one box) Item score
Question Yes Unclear No
I – Information about the medicinal product and treatment
A – Drug information:
Are the following details reported?
1. Drug name (i.e. International Nonproprietary Name INN or generic name)
2. Brand name and/or manufacturer
B – Therapeutic regimen
Are the following details reported?
3. Daily dose and dosing regimen
4. Route of administration (i.e. oral, subcutaneous, . . .)
5. Length of treatment period (dates and duration of treatment)
II – Patient history, diagnosis, medical condition(s) and medications
A – Patient history
Are the following details reported?
6. Age
7. Sex
B – Diagnosis
8. Is the diagnosis for which the suspected drug was administered stated?
C – Concurrent diseases and/or medical conditions:
9. Are concurrent diseases and/or medical conditions reported (including and allergies)? (If explicitly stated that there
were none, give 2 points)
10. Are concurrent diseases analysed/considered with regards to their relevance to the AE?
(Give 2 points if considered in respect to AE Or explicitly stated there are no concurrent diseases, give 1 point if mentioned
but not adequately discussed and 0 point if not reported at all)
D – Concomitant medications
11. Are concomitant medications documented? (if it is explicitly stated that there were none, give 2 points. 1 point if
inadequately reported or unclear and 0 point if no mention of concomitant medications)
12. Are doses, therapeutic regimes and treatment duration reported for concomitant medication? (all the information
is required to score 2 points or if explicitly stated there were no concomitant medications, give 1 point if one or two of the
information is reported otherwise give 0 point)
13. Is the involvement of concomitant medications with AE considered/discussed in the report? (give 2 points if
reported and discussed or stated there were no concomitant medications, 1 point if mentioned but not adequately
discussed, 0 point if not reported)
III – Adverse event/drug interaction information
14. Is the AE/interaction described?
15. Is it reported how the AE (or drug interaction) was diagnosed using appropriate diagnostic tests (including lab
tests)?
Does the report state that the procedures listed below were carried out or explicitly

state that they were not?
16. Dechallenge or dose manipulation (give 2 points if either is reported and patients response discussed or explicitly
stated that there was no dechallenge and 0 point if not reported at all)
17. Rechallenge (give 2 points if dose, name of drug or class of drug for rechallenge is reported and adequately discussed or
if stated that rechallenge was unacceptable, dangerous or unethical, 0 point if not reported at all)
18. Is there a description of the Algorithm/instrument/scale used for causality assessment (i.e. WHO classification, any
other published scale, or authors own clinical judgment)
Herbal preparation information:
Are the following details reported?
1. Full taxonomic name of the plant
2. Plant source (i.e. folium, radix, rhizome, . . .)
3. Extract name and/or manufacturer or brand name (all the information is required to score 2 points, give 1 point if one
or two of the information is reported otherwise give 0 point)
Total Score /38
Scoring instructions
Give a score of 2 points for each “yes” or 1 point for each “unclear” and 0 point for each “no”.
Some questions have additional scoring instructions.